The persistence of cognitive deficits in remitted and unremitted ADHD: a case for the state-independence of response inhibition

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Background: Response inhibition, working memory, and response variability are possible endophenotypes of ADHD based on their association with the disorder and evidence of heritability. One of the critical although rarely studied criteria for a valid endophenotype is that it persists despite waxing and waning of the overt manifestations of the disorder, a criterion known as state-independence. This study examined whether these aspects of cognition exhibit state-independence in ADHD. **Methods:** One hundred and seventy-nine children diagnosed with ADHD in a rigorous baseline assessment were contacted for follow-up assessment in adolescence. Of this sample, 130 (73%) were reascertained. At follow-up, children previously diagnosed with ADHD were identified as remittent ($n = 24$), persistent ($n = 64$), or in partial remission ($n = 42$) based on symptoms and impairment of the disorder. Response inhibition, working memory, and response variability were assessed both in childhood (baseline) and adolescence (follow-up) and were compared with age-matched controls (40 children and 28 adolescents) seen at either time point. **Results:** Relative to controls, ADHD children showed baseline deficits in response inhibition, working memory, and response variability. Only the group difference in response inhibition remained significant in adolescence. In general, cognitive performance among ADHD participants improved with age and did so regardless of changes in ADHD symptoms and impairment. Within the ADHD group, however, cognitive performance in childhood and in adolescence did not differ amongst those with persistent, remittent, and partially remittent forms of the disorder. **Conclusions:** Results demonstrate that response inhibition not only distinguishes ADHD children from their unaffected peers but is also state-independent, such that deficits remain present irrespective of changes in the disease phenotype. In other words, inhibitory deficits measured in childhood persist into adolescence even when the ADHD phenotype remits. These findings provide further evidence that the ability to stop prepotent actions is an endophenotype of ADHD. **Keywords:** ADHD, endophenotype, inhibition, working memory, response variability.

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a prevalent disorder of development, affecting 5% of children worldwide (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Defined by impairing and developmentally atypical levels of inattention and hyperactivity-impulsivity, ADHD is a clinically heterogeneous disorder characterized by high heritability ($h^2 = .80$) (Thapar, Harrington, Ross, & McGuffin, 2000). Like other complex diseases, ADHD appears to conform to a multifactorial polygenetic threshold model of inheritance in which multiple genes, both rare and common, act additively or interactively with environmental factors to give rise to the overt manifestations of the disorder (Cortese, Faraone, & Sergeant, 2011).

The largest genome-wide association study to date has not identified any genome-wide significant findings (Franke, Neale, & Faraone, 2009; Neale et al., 2010). Identification of the genetic contributions to ADHD is likely complicated by phenotypic and genetic heterogeneity, low penetrance, and limited statistical power. One way to enhance power for genetic discovery is to reduce heterogeneity by use of endophenotypes. Endophenotypes are biological traits that mediate the association between some of the genetic risks for a disease and the disease phenotype and which have a genetic architecture that is presumed to be less complex than that of the disorder itself (Gottesman & Gould, 2003; Szatmari et al., 2007). To be useful, endophenotypes should be associated with the disorder, share genetic risk with the disease phenotype, be evident in relatives of affected probands due to increased genetic risk, and be heritable (Crosbie, Pérusse, Barr, & Schachar, 2008; Kendler & Neale, 2010). Valid endophenotypes also should persist despite waxing and waning of the disease phenotype if they are in the causal pathway from gene to disease (state-independence) rather than being a consequence of disease (para-phenotypes).

Several candidate endophenotypes of ADHD have been put forward – including aspects of brain structure and physiology, arousal, motor control, motivation, and cognition (Doyle et al., 2005). Presently, the most common endophenotypes under consideration are neuropsychological markers of executive control. Included are response inhibition, which is

the ability to stop prepotent actions (Barkley, 1997), working memory, which is the ability to rehearse and manipulate information held in mind (Baddeley, 1992) and response variability, which may reflect one's ability to maintain a consistent level of attention or executive control (Unsworth, Redick, Lakey, & Young, 2010; West, Murphy, Armilio, Craik, & Stuss, 2002). Deficits in these skills are commonly observed in children and adults with ADHD (Lipszyc & Schachar, 2010; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005), are present in family members of ADHD probands who do not manifest the disorder (Gau & Shang, 2010; Rommelse et al., 2008; Schachar et al., 2005; Slaats-Willemse, Swaab-Barneveld, De Sonneville, van der Meulen, & Buitelaar, 2003; Uebel et al., 2010), and are at least partially attributable to genetic variation between individuals (Kuntsi et al., 2006; Schachar, Forget-Dubois, Dionne, Boivin, & Robaey, 2011; Vernon, 1989).

The aforementioned evidence suggests that response inhibition, working memory, and response variability are markers of genetic risk for ADHD; however, the extent to which these skills are state-independent has been rarely investigated. In the present study, we investigated the state-independence of these skills by assessing ADHD individuals in childhood and again in adolescence and comparing performance amongst persistent, remittent, and partially remitted subgroups. ADHD individuals also were compared with age-matched controls seen at one time point (i.e., childhood or adolescence). We predicted that ADHD individuals would perform more poorly than controls in childhood and would continues to do so in adolescence regardless of whether they continued to have ADHD. We further predicted that the performance of ADHD individuals would improve between childhood and adolescence, as these skills are refined as children age (Eckert & Eichorn, 1977; McAuley & White, 2011), but that the extent of improvement would be comparable amongst those with persistent, remittent, and partially remitted forms of the disorder.

Method
Participants

One hundred and seventy-nine children diagnosed with ADHD in an outpatient clinic were followed into adolescence, at which point 130 (73%) assented to reassessment. Comparison of baseline measures showed that children who were re-assessed were more impaired [$t(176) = -2.50$, $p = .02$] and slightly more inattentive [$t(176) = -1.95$, $p = .05$] than children who were not re-assessed, although the groups were comparable across a wide range of other clinical variables and demographic factors ($ps > .10$). Two control groups of individuals who did not have ADHD

were recruited via local advertisements: one matched in age to the ADHD group when seen in childhood, the other matched in age to the ADHD group when seen in adolescence. Participants in the ADHD and control groups were primarily middle-class Caucasians and were similar with respect to family intactness, parental employment status, and paternal level of education ($ps > .10$) – although control children had mothers with a higher level of education than ADHD children [$\chi^2 (1, N = 167) = 5.09$, $p = .02$]. Control participants were recruited continuously between baseline and follow-up and were seen only once. For all participants, exclusion criteria were history of (a) pervasive developmental disorder or psychosis, (b) traumatic brain injury with loss of consciousness, (c) uncorrected hearing or visual impairment on screening tests, (d) IQ below 80, and (e) concurrent treatment with medication other than a stimulant and/or treatment with medication within 24 hr of testing.

At baseline, a child was considered to have ADHD when he or she exhibited six or more impairing symptoms of inattention or hyperactivity-impulsivity per the report of either the parent using the Parent Interview for Child Symptoms (Ickowicz et al., 2006) or teacher using the Teacher Telephone Interview (Tannock, Hum, Masellis, Humphries, & Schachar, 2002) and four or more impairing symptoms of inattention or hyperactivity-impulsivity per the report of the other informant (e.g., teacher or parent). Amongst children diagnosed with ADHD, 33 were inattentive, 22 were hyperactive-impulsive, and 75 were combined type. At follow-up, participants were categorized into subgroups based on symptoms and impairment associated with the disorder. A symptom was considered present if it was endorsed at a threshold level by either the parent or adolescent using the Kiddie-Sads-Present and Lifetime Version (Kaufman et al., 1997). Impairment was assessed by the clinician using the Children's Global Assessment Scale (Shaffer et al., 1983) with a cutoff below 60 considered to indicate dysfunction (Bird et al., 1990). In adolescence, 64 participants were considered to have persistent ADHD (i.e., six or more inattentive or hyperactive-impulsive symptoms and CGAS <60): 35 were inattentive, 2 were hyperactive-impulsive, and 27 were combined type. Forty-two participants had partially remittent ADHD, which included 22 participants who had threshold symptoms but minimal impairment (remitted impairment) and 20 who were impaired but had few symptoms (remitted symptoms). A fully remittent group of 24 adolescents had symptoms and impairment that both fell below threshold [Symptoms and impairment were below threshold but remained higher than levels in the control group, which may suggest that symptoms and impairment rarely normalize to control levels even amongst people who outgrow the disorder. A review by Ramos-Quiroga and Casas (2011) discusses the

complexities that are inherent in defining disorder remittance (e.g., reduction vs. normalization of the clinical phenotype).] Our comparison group consisted of 68 age-matched controls (40 children and 28 adolescents). None of the controls had ADHD and few had any other Axis-1 disorder (oppositional defiant = 1, conduct = 1, mood = 2, conduct and mood = 1, anxiety = 4). Participant characteristics are presented in Table 1.

Procedure

At baseline, informed consent was obtained from the child and parent and then the child underwent testing while the parent completed a semistructured clinical interview. The child's teacher was interviewed by phone. Follow-up occurred 5 years after the baseline assessment, on average, which permitted examination of clinical and cognitive variables upon the transition into adolescence. Our follow-up protocol was similar to that just described except that information regarding mental health concerns was obtained from parents and adolescents. Adolescents were asked to refrain from taking stimulant medication 48 hr prior to follow-up (if possible) and to ensure that they were stimulant-free for a minimum of 24 hr before their appointment. At follow-up, the proportion of ADHD participants who reported current use of medication for symptom management was as follows: persistent = 44%, remitted symptoms = 20%, remitted impairment = 41%, fully remittent = 8%. Five adolescents continued taking nonstimulant medication for ethical reasons; however, their exclusion from analyses had no effect on results. All diagnoses at baseline and at follow-up were made by a child psychiatrist and/or clinical psychologist based on criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (American Psychiatric Association, 1994). Ethics approval was granted by the Research Ethics Board at the Hospital for Sick Children.

Cognitive measures

Response inhibition and response variability. The stop signal task assessed response inhibition and response variability (Logan, Cowan, & Davis, 1984). Go trials (75%) required that children make a speeded key press response to letters that appeared on a computer screen, whereas stop trials (25%) required that they inhibit this response when the letter was followed by a tone. 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. Variability in the mean time taken to respond to the letters indexed response variability (GoRTSD). The mean delay of the stop signal less the mean time taken to respond to the letters indexed response inhibition (SSRT).

The stop signal task has high internal consistency ($\alpha > .80$ for GoRTSD and SSRT) (Bedard et al., 2002).

Verbal working memory. Verbal working memory was assessed using the digit span task from the Wechsler Intelligence Scale for Children – 3rd Edition (WISC-III; Wechsler, 1991). Children were read increasingly long number sequences and the total number of items correctly recalled in backward order served as a measure of verbal working memory (DSB). Results were unchanged when the number of items correctly recalled in forward order was controlled (e.g., using difference or residual scores). Reliability of the digit span task is .73.

Spatial working memory. Spatial working memory was assessed using the spatial span task from the Wechsler Intelligence Scale for Children – 3rd Edition as a Process Instrument (WISC-III PI; Kaplan, Fein, Kramer, Delis, & Moris, 1999). Children were shown increasingly long sequences of spatial locations and the total number of items correctly recalled in backward order served as an index of spatial working memory (SSB). Results were unchanged when the number of items correctly recalled in forward order was controlled (e.g., using difference or residual scores). Reliability of the spatial span task is .75.

Analytic approach

Data were invalid/missing for 10 participants in the Stop Signal task, 18 participants in the Digit Span task (due to recent administration of the WISC), and 28 participants in the Spatial Span task (which was added after their enrollment in the study). Data were assumed to be missing at random and were replaced using multiple imputation with auxiliary variables using LISREL 8.80 (Jöreskog & Sörbom, 1993). Repeated measures ANOVAs were used to examine age-related change in the performance of our ADHD subgroups. This enabled us to determine whether response inhibition, working memory, and response variability improved over time and, if so, whether the extent of improvement varied as a function of change in the disorder phenotype. One-way ANOVAs with planned contrasts also were used at baseline and follow-up to test the hypothesis that performance did not vary amongst ADHD subgroups but was worse overall than that of controls. Specific comparisons included (a) our partially remitted subgroups, (b) our partially remitted subgroups versus our persistent subgroup, (c) our partially remitted and persistent subgroups versus our fully remittent subgroup, (d) all ADHD versus controls. A priori power analyses using medium to large effect sizes (e.g., Lipszyc & Schachar, 2010; Martinussen et al., 2005), alpha of .05, and power of .80 indicated that 80–200 participants were required for the one-way ANOVAs, which is likely an overestimate given our use of planned

Table 1 Participant characteristics at baseline and follow-up

	ADHD				Control		Overall comparison		
	Remittent	Remitted Impairment	Remitted Symptoms	Persistent	Younger	Older	F	η^2	Significant effects
N (Male %)	24 (67%)	22 (73%)	20 (80%)	64 (78%)	40 (38%)	28 (50%)	10.55[b],**	.20[b]	R,RI,RS,P>YC,OC[a]
Full scale IQ	106.6 (11.3)	107.9 (16.1)	101.2 (14.3)	102.8 (15.4)	119.8 (11.3)	117.5 (12.4)	5.90[c],**	.13[c]	R/RI/RS/P<YC[b]
									R/RI/RS/P<OC[c]
Baseline variables									
Age	8.6 (2.0)	9.0 (1.5)	8.8 (2.0)	9.0 (1.7)	8.5 (1.2)	NA	.61	.01	
Age range	6.3–15.3	6.9–13.3	6.4–12.8	6.3–12.8	6.8–10.6	NA			
Impairment	57.3 (10.8)	55.3 (7.6)	49.0 (5.9)	49.8 (7.9)	93.3 (6.)	NA	223.28**	.84	RS<RI, RS/RI/P<R, R/RI/RS/P<YC
Inattentive symptoms	7.0 (1.5)	7.7 (1.2)	6.9 (1.8)	7.9 (1.3)	.28 (.88)	NA	919.22**	.85	R/RI/RS/P>YC
Hyperactive-impulsive symptoms	6.5 (2.0)	6.4 (2.4)	6.4 (2.3)	7.3 (2.0)	.30 (.72)	NA	92.69**	.69	R/RI/RS/P>YC
Response Variability	206.3 (66.0)	228.1 (42.2)	251.9 (88.1)	230.7 (72.8)	201.7 (74.9)	NA	2.26[†]	.05	R/RI/RS/P>YC
Response inhibition	322.4 (148.8)	341.6 (105.6)	422.6 (158.6)	362.3 (166.2)	290.4 (82.8)	NA	3.46*	.08	R/RI/RS/P>YC
Verbal working memory	3.8 (1.2)	3.9 (1.8)	3.4 (1.6)	4.3 (2.6)	5.6 (2.1)	NA	4.87*	.11	R/RI/RS/P<YC
Spatial working memory	4.6 (1.9)	4.0 (1.9)	3.9 (1.7)	4.1 (2.0)	6.0 (1.8)	NA	8.31**	.17	R/RI/RS/P<YC
Follow-up variables									
Age	14.3 (1.9)	14.1 (1.8)	14.1 (1.8)	13.7 (1.5)		13.6 (1.8)	.90	.02	
Age range	10.8–19.2	10.9–17.2	11.6–18.3	11.1–18.0		10.8–16.5			
Impairment	72.5 (8.2)	65.1 (4.5)	50.4 (6.9)	52.6 (5.5)		94.6 (1.9)	312.14**	.89	RS<RI, RS/RI>P, RI/RS/P<R, R/RI/RS/P<OC
Inattentive symptoms	2.9 (1.5)	7.5 (1.3)	3.3 (1.7)	7.9 (1.4)		.50 (.75)	190.36**	.83	RS<RI, RS/RI<P, RS/RI/P>R, R/RI/RS/P>OC
Hyperactive-impulsive symptoms	2.0 (1.6)	3.9 (2.6)	1.7 (1.8)	4.9 (3.0)		.11 (31)	25.55**	.40	RS<RI, RS/RI<P, RS/RI/P>R, R/RI/RS/P>OC
Response variability	132.1 (30.6)	134.0 (32.4)	152.8 (33.5)	148.6 (41.2)		141.3 (46.0)	1.51	.04	
Response inhibition	244.6 (83.8)	258.2 (76.9)	268.3 (64.6)	250.1 (77.6)		212.9 (54.8)	2.08[†]	.05	R/RI/RS/P>OC
Verbal working memory	7.7 (2.3)	7.6 (2.0)	6.8 (2.2)	7.5 (2.5)		7.2 (2.3)	.54	.01	
Spatial working memory	7.6 (2.2)	7.2 (2.2)	7.4 (2.0)	7.5 (2.1)		7.6 (1.3)	.20	.01	

Means (standard deviations) of clinical and cognitive measures. R, remittent; RI, remitted impairment; RS, remitted symptoms; P, Persistent; NA, not applicable.
[a]Chi square comparison of all subgroups. [b]/[c]One-way ANOVA with planned contrasts of ADHD subgroups and Younger Controls (YC)/Older Controls (OC). The *F* statistic is based on $n = 170$ for analyses involving ADHD and YC and $n = 158$ for analyses involving ADHD and OC. *$p < .05$; **$p < .001$; [†]$p < .10$.

contrasts. It was not possible to obtain effect size estimates for comparisons of the ADHD subgroups; however, if one were to assume that subgroup differences were small in magnitude, as reported in other follow-up studies (e.g., Biederman et al., 2009; Halperin, Trampush, Miller, Marks, & Newcorn, 2008), then thousands of ADHD individuals would be required to conclude that the null findings of our repeated measures ANOVAs were actually significant.

Results

As shown in Figure 1, repeated measures ANOVAs of the ADHD subgroups revealed a significant main effect of time for response inhibition [$F(1, 126) = 52.38$, $\eta^2 = .29$, $p < .001$], verbal working memory [$F(1, 126) = 235.46$, $\eta^2 = .65$, $p < .001$], spatial working memory [$F(1, 126) = 173.71$, $\eta^2 = .58$, $p < .001$], and response variability [$F(1, 126) = 157.00$, $\eta^2 = .55$, $p < .001$]. There was a group trend for response variability [$F(3, 126) = 2.42$, $\eta^2 = .05$, $p = .07$] but not for any other cognitive measure (ps > .10). In no instance was the time × group interaction significant (ps > .10).

Main effects of the one-way ANOVAs of ADHD subgroups and controls are presented in Table 1. At each time point, main effects were evaluated at an adjusted alpha of .0125 to reflect examination of four different outcome measures. Planned contrasts revealed no significant differences among ADHD subgroups at baseline or follow-up (ps > .05). At baseline, contrasts of the entire ADHD sample and controls showed that ADHD children performed more poorly than control children on measures of response inhibition [$t(165) = 2.76$, $d = .43$, $p = .01$], verbal working memory [$t(165) = -4.29$, $d = -.67$, $p < .001$), spatial working memory [$t(165) = -5.41$, $d = -.84$, $p < .001$], and response variability [$t(165) = 2.07$, $d = .32$, $p = .04$]. Only the difference between ADHD and control adolescents in response inhibition remained significant at follow-up [$t(153) = 2.71$, $d = .44$, $p = .01$; all other ps > .50]. These results were further explored by running additional analyses, the details of which are available as online supplementary material. (See Appendix S1 and Table S1).

Discussion

Few prospective follow-up studies of ADHD have examined cognition as a function of disorder persistence. Extant research has shown that adolescents with childhood histories of ADHD perform more
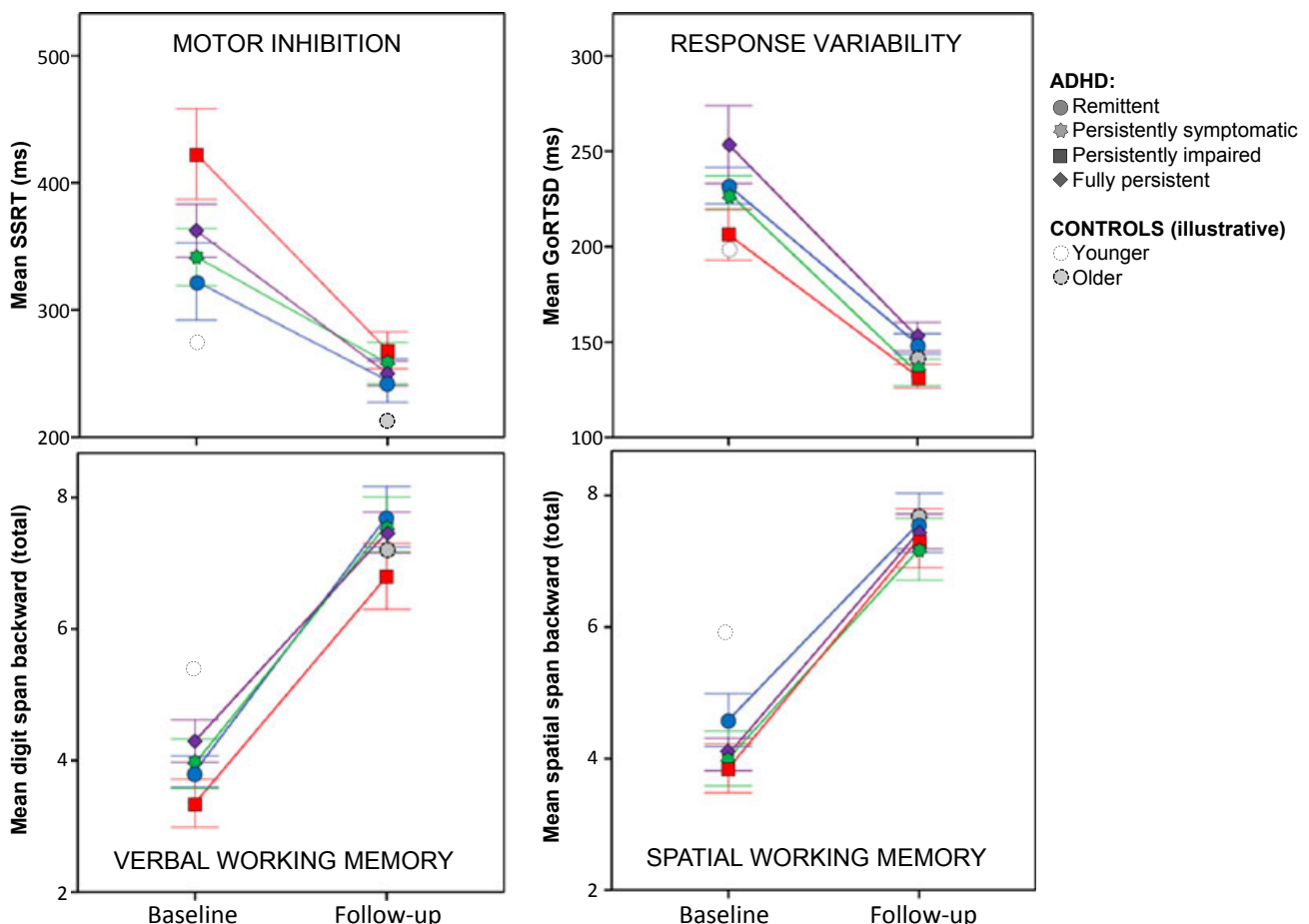

Figure 1 Time-related change in cognitive abilities as a function of ADHD remission status at follow-up. Control groups are included for illustrative purposes only

poorly than controls on a composite of neuropsychological measures and that this composite does not vary with remission status at follow-up (Biederman et al., 2009). Similar findings have been reported for measures of target detection, processing speed, response variability, interference control, working memory, and ankle actigraph activity (Bedard, Trampush, Newcorn, & Halperin, 2010; Halperin et al., 2008; Vaughan et al., 2011). At least one study has reported a lack of association between parent and adolescent ratings of ADHD symptoms at follow-up and performance on a task purported to measure response inhibition – although the inhibitory demands imposed by the task were unclear (Bedard et al., 2010).

A trait that exhibits state-independence may mark underlying genetic risk because it remains evident irrespective of changes in the overt manifestations of the disorder – being observable, for example, prior to disease onset, at varying levels of symptom severity, following successful treatment of the disorder, and in instances in which the disorder morphs into another clinical phenomenon. A trait that waxes and wanes with the disease phenotype is more likely to be an epiphenomenon of the disorder rather than in the causal pathway. In our study, ADHD children showed significant deficits in response inhibition, working memory, and response variability relative to their non-ADHD peers, confirming previous findings. When ADHD and controls were compared in adolescence, however, only the difference in response inhibition remained significant. At neither time point did response inhibition, working memory, or response variability vary significantly across ADHD subgroups defined by remission status. And, though all ADHD subgroups demonstrated age-related improvement in these aspects of cognition, the extent of improvement was comparable for those with persistent, remittent, and partially remitted forms of the disorder. Thus, not only does the ability to stop prepotent actions distinguish ADHD individuals from their unaffected peers, but it is also state-independent, such that deficits persist regardless of the course of the disorder.

Response inhibition has been posited to be a core feature of ADHD (Barkley, 1997), which some argue reflects an inherent tendency to 'act without thinking'. Although not all individuals with ADHD exhibit a deficit in response inhibition, a recent meta-analysis reported an effect size of .62 for SSRT in ADHD relative to controls (Lipszyc & Schachar, 2010). Among ADHD individuals, there was no significant effect of overall response time or response variability on SSRT effect size, which indicates that deficient inhibition is not simply attributable to a faulty 'go' process. The SSRT effect size in ADHD was comparable to that of individuals with obsessive compulsive disorder and schizophrenia, but was negligible in individuals with other kinds of pathology (e.g., mood and anxiety disorders, reading disorder, oppo-

sitional defiant disorder/conduct disorder) – which suggests that it is ADHD, and not comorbidities, that is associated with the inhibitory deficit we observed in our study. It is worth noting that response inhibition may still be a valid endophenotype of ADHD even though deficits are not observed in all ADHD individuals and are sometimes observed in individuals with non-ADHD diagnoses. This may occur, for example, if some carriers of ADHD susceptibility genes experience reduced penetrance and if genetic risk for ADHD is shared with other disorders (Crosbie et al., 2008). Because ADHD is highly heterogeneous, it may also be the case that response inhibition is one of several valid endophenotypes for a subgroup of individuals with ADHD rather than everyone with the disorder.

Mounting evidence suggests that response inhibition is a marker of genetic risk for ADHD. For example, response inhibition shows a pattern of familial aggregation, such that poor inhibitors are likely to have a stronger family history of ADHD than good inhibitors (Crosbie & Schachar, 2001). In addition, unaffected relatives of ADHD probands tend to inhibit their responses less effectively than individuals who do not have a first degree relative with the disorder – regardless of whether or not they exhibit ADHD themselves (Schachar et al., 2005). Twin studies have further demonstrated that response inhibition is heritable (Schachar et al., 2011), whilst recent genetic work has shown that individual differences in SSRT may be predicted by polymorphisms of the dopamine transporter gene (Cummins et al., 2011). The results of our study add to this literature by demonstrating that response inhibition also exhibits trait-like properties: not only do youth with ADHD show a deficit in response inhibition relative to their non-ADHD peers, but this deficit remains stable irrespective of disorder persistence. These findings, in conjunction with previous work, provide further validation that response inhibition may be an endophenotype of ADHD.

Working memory has also been posited to play a central role in ADHD (Martinussen et al., 2005). Although our children with ADHD demonstrated working memory deficits compared with their non-ADHD peers, this deficit appeared to normalize in adolescence. Previous research has hinted that deficits in working memory may become less strongly associated with ADHD during development (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Hervey, Epstein, & Curry, 2004; Martinussen et al., 2005) and may persist only in individuals with a persistent – thought not remittent – course of the disorder (Halperin et al., 2008). Our results suggest that children with ADHD may outgrow their working memory deficits over time; however, other interpretations should be acknowledged. One possibility is that the tasks used in our study were insufficiently complex to tax the working memory system or posed working memory demands that varied across devel-

opment. This seems unlikely, however, given that tasks requiring the re-sequencing of information converge with more complex working memory tasks derived from the cognitive literature (e.g., operation span, listening span, n-back; Lewandowsky, Oberauer, Yang, & Ecker, 2010) and that other studies have failed to find working memory deficits in adolescents and adults with ADHD even when tasks with ostensibly stronger working memory demands have been used (Hill et al., 2010; Valera, Faraone, Biederman, Poldrack, & Seidman, 2005). Another possibility is that adolescents with ADHD experienced practice effects by virtue of completing the working memory tasks in childhood and adolescence. Given the stability of these tasks over considerably shorter periods of time (e.g., Wechsler, 1991), this explanation also seems unlikely. Furthermore, it is unclear why practice effects would not also result in substantive gains on the stop-signal task when re-administered to ADHD adolescents at follow-up, which was not the case.

Although children with ADHD were more variable than control children at baseline, ADHD adolescents responded with a similar level of consistency on the stop signal task as their age-matched peers at follow-up. Intraindividual variability has been described as one of the most striking features of ADHD (Castellanos & Tannock, 2002), yet it is a behavioral phenomenon that lacks clear cognitive or neural correlates. Moment-to-moment fluctuations in performance have been ascribed to lapses in attention (Leth-Steensen, Elbaz, & Douglas, 2000; Spencer et al., 2009), failures to maintain executive control (West et al., 2002), and difficulties with temporal processing (Toplak & Tannock, 2005) – the causes of which are likely to be multiply determined and are not, at present, well-understood (MacDonald, Nyberg, & Backman, 2006). In contrast with our findings, one follow-up study reported that young adults with childhood histories of ADHD continued to demonstrate greater variability in response speed on a continuous performance task (CPT) compared with healthy controls irrespective of whether they were remittent or persistent for the disorder (Halperin et al., 2008). One possible explanation for this discrepancy pertains to differences in the tasks that were used. The stop signal task invites on-line adjustments in performance to maximize the tradeoff between responding quickly on go trials and being able to withhold that response on stop trials – a requirement that is not embodied in many other reaction time (RT) measures, including the CPT. For this reason, our results do not negate the possibility that response variability is an endophenotype of ADHD. Rather, it may be the case that other kinds of RT tasks are more suitable endophenotypes of the disorder.

In summary, previous work has demonstrated that response inhibition is heritable, familial, and shows a robust association with ADHD. The present study makes an important contribution to this literature by following a rigorosly diagnosed cohort of ADHD youth prospectively over time – thus enabling us to examine the extent to which response inhibition exhibits state-independence. Our data show that inhibitory deficits persist in individuals with childhood histories of ADHD irrespective of changes in disease severity, further supporting the view that response inhibition is a valid endophenotype of ADHD. However, these results should be interpreted in the context of limitations to our study. Because our ADHD group represents a primarily Caucasian middle-class sample, our findings may not generalize to ADHD individuals drawn from other ethnic and/or socioeconomic groups. Moreover, our findings may be biased by virtue of the fact that ADHD adolescents were compared with a relatively small group of control adolescents who were seen at only one time point and adolescent self-report was the only method used to assess compliance with the medication washout period prior to re-assessment – thus raising the possibility that our follow-up results reflect practice effects and/or pharmacological enhancement of cognitive performance.

In addition to addressing these limitations, an important avenue for future research is examining whether response inhibition holds an intermediate position in a causal pathway linking underlying susceptibility genes to the inattentive and hyperactive-impulsive traits that constitute the overt manifestations of ADHD or is better conceptualized by other causal models of the disorder (e.g., Coghill, Rhodes, Grimmer, & Matthews, 2013). Although the assumption of causality is implicit in many conceptualizations of endophenotypes, it has been noted that this assumption is seldom made explicit or tested empirically (Kendler & Neale, 2010). The test of mediation of genetic risk by any endophenotype requires knowledge of genetic risks for disease. Given the high base rate of ADHD and the fact that response inhibition can be reliably measured with inexpensive behavioral paradigms (such as the stop signal task), future studies using longitudinal twin data hold much promise in differentiating between models of causality and genetic pleiotropy and thus furthering our understanding of the genetic basis for this relatively common and chronically disabling condition.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Homogeneity of variance of the cognitive measures.
Table S1. Correlations between diagnostic criteria.

Acknowledgments

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Key points

- Endophenotypes are markers of genetic risk that are assumed to be genetically simpler than disorder phenotypes and thus may increase power for genetic discovery
- Response inhibition has been identified as a possible endophenotype of ADHD because it is heritable, shows association with the disorder, and is present in unaffected family members
- Our results show that response inhibition is also state-independent – such that a deficit persists in ADHD irrespective of the course of the disorder
- This study suggests that individuals with ADHD may experience long-standing difficulties related with the regulation of their behavior, even if they appear to outgrow the disorder, and thus supports the view that response inhibition a valid endophenotype of ADHD

References

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders*, 4th ed. Washington, DC: American Psychiatric Association.

Baddeley, A. (1992). Working memory. *Science, 255*, 556–559.

Barkley, R.A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin, 121*, 65–94.

Bedard, A.C., Nichols, S., Barbosa, J.A., Schachar, R., Logan, G.D., & Tannock, R. (2002). The development of selective inhibitory control across the life span. *Developmental Neuropsychology, 21*, 93–111.

Bedard, A.C., Trampush, J.W., Newcorn, J.H., & Halperin, J.M. (2010). Perceptual and response inhibition in adolescents/young adults with childhood-diagnosed ADHD. *Neuropsychology, 24*, 424–434.

Biederman, J., Petty, C.R., Ball, S.W., Fried, R., Doyle, A.E., Cohen, D., … & Faraone, S.V. (2009). Are cognitive deficits in attention deficit/hyperactivity disorder related to the course of the disorder? A prospective controlled follow-up study of grown up boys with persistent and remitting courses. *Psychiatry Research, 170*, 177–182.

Bird, H.R., Yager, T.J., Staghezza, B., Gould, M.S., Canino, G., & Rubio-Stipec, M. (1990). Impairment in the epidemiological measurement of childhood psychopathology in the community. *Journal of the American Academy of Child and Adolescent Psychiatry, 29*, 796–803.

Boonstra, A.M., Oosterlaan, J., Sergeant, J.A., & Buitelaar, J.K. (2005). Executive functioning in adult ADHD: A meta-analytic review. *Psychological Medicine, 35*, 1097–1108.

Castellanos, F.X., & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. *Nature Reviews Neuroscience, 3*, 617–628.

Coghill, D.H., Rhodes, S.M., Grimmer, C., & Matthews, K. (2013). A longitudinal examination of neuropsychological and clinical functioning in boys with attention deficit hyperactivity disorder (ADHD): Improvements in executive functioning do not explain clinical improvement. *Psychological Medicine*. [Epub ahead of print].

Cortese, S., Faraone, S.V., & Sergeant, J. (2011). Misunderstandings of the genetics and neurobiology of ADHD: Moving beyond anachronisms. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 156*, 513–516.

Crosbie, J., Pérusse, D., Barr, C.L., & Schachar, R. (2008). Validating psychiatric endophenotypes: Inhibitory control and attention deficit hyperactivity disorder. *Neuroscience and Biobehavioral Reviews, 32*, 40–45.

Crosbie, J., & Schachar, R. (2001). Deficient inhibition as a marker for familial ADHD. *American Journal of Psychiatry, 158*, 1884–1890.

Cummins, T.D., Hawi, Z., Hocking, J., Strudwick, M., Hester, R., Garavan, H., … & Bellgrove, M. (2011). Dopamine transporter genotype predicts behavioural and neural measures of response inhibition. *Molecular Psychiatry, 17*, 1086–1092.

Doyle, A.E., Willcutt, E.G., Seidman, L.J., Biederman, J., Chouinard, V.A., Silva, J., & Faraone, S.V. (2005). Attention-Deficit/Hyperactivity Disorder endophenotypes. *Biological Psychiatry, 57*, 1324–1335.

Eckert, H.M., & Eichorn, D.H. (1977). Developmental variability in reaction time. *Child Development, 48*, 452–458.

Franke, B., Neale, B.M., & Faraone, S.V. (2009). Genome-wide association studies in ADHD. *Human Genetics, 126*, 13–50.

Gau, S.S., & Shang, C. (2010). Executive functions as endophenotypes in ADHD: Evidence from the Cambridge Neuropsychological test battery (CANTAB). *Journal of Child Psychology and Psychiatry, 51*, 838–849.

Gottesman, I.I., & Gould, T.D. (2003). The endophenotype concept in psychiatry: Etymology and strategic intentions. *The American Journal of Psychiatry, 160*, 636–645.

Halperin, J.M., Trampush, J.W., Miller, C.J., Marks, D.J., & Newcorn, J.H. (2008). Neuropsychological outcome in adolescents/young adults with childhood ADHD: Profiles of persisters, remitters and controls. *Journal of Child Psychology and Psychiatry, 49*, 958–966.

Hervey, A.S., Epstein, J.N., & Curry, J.F. (2004). Neuropsychology of adults with attention-Deficit/Hyperactivity disorder: A meta-analytic review. *Neuropsychology, 18*, 485–503.

Hill, B.D., Elliott, E.M., Shelton, J.T., Pella, R.D., O'Jile, J.R., & Gouvier, W.D. (2010). Can we improve the clinical assessment of working memory? An evaluation of the Wechsler Adult Intelligence Scale-Third Edition using a working memory criterion construct. *Journal of Clinical Experimental Neuropsychology, 32*, 315–323.

Ickowicz, A., Schachar, R., Sugarman, R., Chen, S., Millette, C., & Cook, L. (2006). The parent interview for child symptoms (PICS): A situation-specific clinical research interview for attention deficit hyperactivity and related disorders. *Canadian Journal of Psychiatry, 50*, 325–328.

Jöreskog, K.G., & Sörbom, D. (1993). *LISREL 8: Structural equation modeling with the SIMPLIS command language*. Lincolnwood, IL: Scientific Software International.

Kaplan, E., Fein, D., Kramer, J., Delis, D., & Moris, R. (1999). *WISC-III as a process instrument*. San Antonio, TX: The Psychological Corporation.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., ... & Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 980–988.

Kendler, K.S., & Neale, M.C. (2010). Endophenotype: A conceptual analysis. *Molecular Psychiatry, 15*, 789–797.

Kuntsi, J., Rogers, H., Swinard, G., Börger, N., van der Meere, J., Rijsdijk, F., & Asherson, P. (2006). Reaction time, inhibition, working memory and 'delay aversion' performance: Genetic influences and their interpretation. *Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences, 36*, 1613–1624.

Leth-Steensen, C., Elbaz, Z.K., & Douglas, V.I. (2000). Mean response times, variability, and skew in the responding of ADHD children: A response time distributional approach. *Acta Psychologica, 104*, 167–190.

Lewandowsky, S., Oberauer, K., Yang, L.X., & Ecker, U.H. (2010). A working memory test battery for MATLAB. *Behavior Research Methods, 42*, 571–585.

Lipszyc, J., & Schachar, R. (2010). Inhibitory control and psychopathology: A meta-analysis of studies using the stop signal task. *Journal of the International Neuropsychological Society, 16*, 1064–1076.

Logan, G.D., Cowan, W.B., & Davis, K.A. (1984). On the ability to inhibit simple and choice reaction time responses: A model and a method. *Journal of Experimental Psychology: Human Perception and Performance, 10*, 276–291.

MacDonald, S.W., Nyberg, L., & Backman, L. (2006). Intra-individual variability in behavior: Links to brain structure, neurotransmission and neuronal activity. *Trends in Neuroscience, 29*, 474–480.

Martinussen, R., Hayden, J., Hogg-Johnson, S., & Tannock, R. (2005). A meta-analysis of working memory impairments in children with attention-Deficit/Hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 44*, 377–384.

McAuley, T., & White, D.A. (2011). A latent variables examination of processing speed, response inhibition, and working memory during typical development. *Journal of Experimental Child Psychology, 108*, 453–468.

Neale, B.M., Medland, S.E., Ripke, S., Asherson, P., Franke, B., Lesch, K.P., ... & Psychiatric GWAS Consortium: ADHD Subgroup. (2010). Meta-analysis of genome-wide association studies of Attention-Deficit/Hperactivity Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*, 884–897.

Polanczyk, G., de Lima, M.S., Horta, B.L., Biederman, J., & Rohde, L.A. (2007). The worldwide prevalence of ADHD: A systematic review and metaregression analysis. *The American Journal of Psychiatry, 164*, 942–948.

Ramos-Quiroga, J.A., & Casas, M. (2011). Achieving remission as a routine goal of pharmacotherapy in attention-deficit hyperactivity disorder. *CNS Drugs, 25*, 17–36.

Rommelse, N.N., Altink, M.E., Oosterlaan, J., Buschgens, C.J., Buitelaar, J., & Sergeant, J.A. (2008). Support for an independent familial segregation of executive and intelligence endophenotypes in ADHD families. *Psychological Medicine, 38*, 1595–1606.

Schachar, R., Crosbie, J., Barr, C.L., Ornstein, T.J., Kennedy, J., Malone, M., ... & Pathare, T. (2005). Inhibition of responses in siblings concordant and discordant for attention deficit hyperactivity disorder. *The American Journal of Psychiatry, 162*, 1076–1082.

Schachar, R., Forget-Dubois, N., Dionne, G., Boivin, M., & Robaey, P. (2011). Heritability of response inhibition in children. *Journal of the International Neuropsychological Society, 17*, 238–247.

Shaffer, D., Gould, M.S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., & Aluwahlia, S. (1983). A children's global assessment scale (CGAS). *Archives of General Psychiatry, 40*, 1228–1231.

Slaats-Willemse, D., Swaab-Barneveld, H., De Sonneville, L., van der Meulen, E., & Buitelaar, J. (2003). Deficient response inhibition as a cognitive endophenotype of ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry, 42*, 1242–1248.

Spencer, S.V., Hawk, L.W., Jr, Richards, J.B., Shiels, K., Pelham, W.E., Jr, & Waxmonsky, J.G. (2009). Stimulant treatment reduces lapses in attention among children with ADHD: The effects of methylphenidate on intra-individual response time distributions. *Journal of Abnormal Child Psychology, 37*, 805–816.

Szatmari, P., Maziade, M., Zwaigenbaum, L., Merette, C., Roy, M.A., Joober, R., & Palmour, R. (2007). Informative phenotypes for genetic studies of psychiatric disorders. *American Journal of Genetics Part B: Neuropsychiatric Genetics, 144B*, 581–588.

Tannock, R., Hum, M., Masellis, M., Humphries, T., & Schachar, R. (2002). *Teacher telephone interview for children's academic performance, attention, behavior, and learning: DSM-IV version (TTI-IV)*. Toronto, Canada: The Hospital for Sick Children.

Thapar, A., Harrington, R., Ross, M., & McGuffin, P. (2000). Does the definition of ADHD affect heritability? *Journal of the American Academy of Child and Adolescent Psychiatry, 39*, 1528–1536.

Toplak, M.E., & Tannock, R. (2005). Tapping and anticipation performance in attention deficit hyperactivity disorder. *Perceptual Motor Skills, 100* (3 Pt 1), 659–675.

Uebel, H., Albrecht, B., Asherson, P., Borger, N.A., Butler, L., Chen, W., ... & Banaschewski, T. (2010). Performance variability, impulsivity errors and the impact of incentives as gender-independent endophenotypes for ADHD. *Journal of Child Psychology and Psychiatry, 51*, 210–218.

Unsworth, N., Redick, T.S., Lakey, C.E., & Young, D.L. (2010). Lapses in sustained attention and their relation to executive control and fluid abilities: An individual differences investigation. *Intelligence, 38*, 111–122.

Valera, E.M., Faraone, S.V., Biederman, J., Poldrack, R.A., & Seidman, L.J. (2005). Functional neuroanatomy of working memory in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*, 439–447.

Vaughan, A.J., Epstein, J.N., Raush, J., Altaye, M., Langberg, J., Newcorn, J., & Wigal, T. (2011). Relation between outcomes on a Continuous Performance Test and ADHD symptoms over time. *Journal of Abnormal Child Psychology, 39*, 853–864.

Vernon, P.A. (1989). The heritability of measures of speed of information-processing. *Personality and Individual Differences, 10*, 573–576.

Wechsler, D. (1991). *Wechsler intelligence scale for children*, 3rd ed. San Antonio, TX: Harcourt Assessment.

West, R., Murphy, K.J., Armilio, M.L., Craik, F.I.M., & Stuss, D.T. (2002). Lapses of intention and performance variability reveal age-related increases in fluctuations of executive control. *Brain and Cognition, 49*, 402–419.