Stimulants and the developing brain

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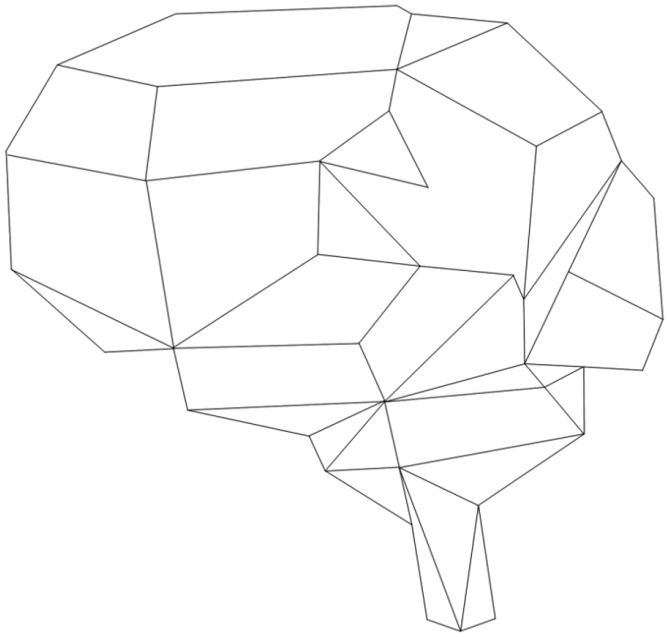
Chapter 9

NO LONG-TERM EFFECTS OF STIMULANT TREATMENT ON ADHD SYMPTOMS, SOCIAL-EMOTIONAL FUNCTIONING, OR COGNITION



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Schweren LJS, Hoekstra PJ, van Lieshout M, Oosterlaan J, Rommelse NNJ, Buitelaar JK, Franke B, Hartman CA. Long-term effects of stimulant treatment on ADHD symptoms, social-emotional functioning, and cognition.

ABSTRACT

Background: Methodological and ethical constraints have hampered research into lasting long-term outcomes of stimulant treatment in individuals with attention-deficit/hyperactivity disorder (ADHD).
Aims: To investigate whether stimulant treatment history predicts long-term development of ADHD symptoms, social-emotional functioning, or cognition, measured after medication wash-out.
Method: Outcomes were measured twice, six years apart, in two ADHD groups (stimulant-treated vs. not stimulant-treated between baseline and follow-up), closely matched on baseline characteristics (n=148, 58% male, age=11.1). A matched healthy control group was included for reference.
Results: All but two outcome measures (emotional problems and prosocial behavior) improved between baseline and follow-up. For all outcomes, improvement over time was the same for participants who had received treatment and those who had not.
Conclusions: Stimulant treatment is not associated with the long-term developmental course of ADHD symptoms, social-emotional functioning, or cognition. These findings are an important source to feed the scientific and public debate.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent and often persistent developmental disorder, characterized by age-inappropriate and impairing levels of inattention and/or hyperactivity-impulsivity. ADHD has been associated with a broad range of neurocognitive deficits, including impaired executive functioning (Willcutt et al., 2005), timing deficits (Noreika et al., 2013), and higher response time variability (Klein et al., 2006). In the majority of individuals with ADHD, stimulants acutely reduce symptoms (Swanson et al., 2001) and improve neurocognitive functioning (Coghill et al., 2014b). Concerns about potential harmful long-term effects of stimulant treatment, as well as anticipation of potential lasting benefits of treatment have dominated the public and scientific debate. Adequately investigating long-term treatment effects, especially in children, is methodologically and ethically challenging, hence evidence for either positive or negative long-term outcomes of stimulant treatment is equivocal. In the Multimodal Treatment Study of ADHD (MTA), the largest controlled treatment study to date, the benefits of 14 months of stimulant treatment on a broad range of outcomes rapidly diminished in subsequent years (MTA Cooperative Group, 1999; Molina et al., 2009; Swanson et al., 2007a). In the MTA study, outcomes were assessed without a medication wash-out phase, which impedes the distinction between lasting effects of prior treatment and acute effects of ongoing treatment. When rated while off-medication, ADHD symptoms were found not to change with one year of stimulant treatment (Huang et al., 2012). Attention task performance and IQ did improve over the course of one year, but in the absence of a comparable non-treated or healthy control group, these changes may reflect normal maturation (Tsai et al., 2013). Observational studies have reported higher ADHD persistence rates in stimulant-treated patients compared to non-treated patients (Biederman et al., 2012; van Lieshout et al., 2016a), while at the same time rates of comorbidity were found to be lower in treated patients (Biederman et al., 2009). Importantly, in these studies confounding-by-indication and self-selection could not satisfactorily be addressed. Here, we applied stringent matching procedures to derive two comparable ADHD samples from a large prospective cohort study (i.e., stimulant-treated and non-stimulant-treated) as well as a typically developing reference group. Outcomes were repeatedly measured over six years, always while participants were in their non-medicated state. We investigated whether stimulant treatment between baseline and follow-up predicted the developmental trajectory of ADHD symptoms, social-emotional functioning, and/or cognition.

METHODS

Participants

Participants were drawn from the prospective multi-centre IMAGE-NeuroIMAGE cohort study (von Rhein et al., 2015a). The full cohort includes 751 children, adolescents, and young adults with ADHD from 590 families. At baseline, ADHD diagnosis was ascertained using the Strengths and Difficulties Questionnaire (van Widenfelt et al., 2003) (SDQ, >90th percentile on the hyperactivity subscale), the parent- and teacher-rated Conners' ADHD scales (CPRS and CTRS; T≥63 on the DSM inattentive or hyperactive/impulsive scale) (Conners et al., 1998a, 1998b) and the Parental Account of Children's Symptoms interview (PACS; ≥6 symptoms, present in ≥2 situations and ≥1 symptom reported by the teacher) (Taylor, 1986). Participants with ≥6 symptoms but who did not fulfill all diagnostic criteria, were classified as subthreshold ADHD. At follow-up, ADHD diagnosis in participants <18 years was ascertained again using the same CPRS and CTRS criteria, complemented with the Schedule for Affective Disorders and Schizophrenia for School-Age Children interview (K-SADS; ≥6 symptoms, present in ≥2 situations, causing impairment, and onset before age 12) (Kaufman et al., 1997). For participants ≥18 years, the self-rated Conners' scale (CAARS; Conners et al., 1999) was used instead of the teacher-rated scale, and five symptoms were sufficient for diagnosis. Participants who scored T≥63 on either of the Conners' scales or had sufficient symptoms, but did not fulfill all diagnostic criteria, were classified as subthreshold ADHD.

Average follow-up time was 5.9 years (SD=0.6), and the retention rate was high (77%). We applied the following inclusion criteria: (1) participation at baseline and follow-up, (2) diagnosis of (subthreshold) ADHD at baseline and/or at follow-up, (3) IQ>70 at baseline and follow-up, and (4) no known genetic or neurological disorders. Eligible participants were split according to treatment between baseline and follow-up into stimulant-treated (n=337) and non-stimulant-treated participants (n=138). Stimulant treatment prior to baseline and treatment with non-stimulant psychoactive medication was allowed in both groups. From the two ADHD groups we selected all participants who had a one-to-one match on gender, age (±<0.5 SD), and baseline number of ADHD symptoms (±<0.5 SD). This resulted in two comparable groups of 74 participants with ADHD each (Table 1).

For reference, a gender- and age-matched healthy control sample was drawn from the IMAGE-NeuroIMAGE cohort as well, applying the same inclusion and matching criteria (except inclusion criterion two/symptom-matching). In addition, control participants had no family-history of any psychiatric disorder. All assessments took place at two sites in the Netherlands. Participants were asked to withhold use of

psychoactive drugs for 48 hours before each assessment. Informed consent was signed by all participants and their parents (only parents signed informed consent for participants < 12 years). Procedures were approved by the local ethical committee of each site.

TABLE 1. Baseline characteristics of the two treatment groups.

	Treated		Non-treated			
	M	**SD**	**M**	**SD**	**Stat.**	**p**
Gender=male	N=43	58.1%	N=43	58.1%	0.000	1.000
Age	11.14	3.29	11.00	3.23	0.066	0.798
Site=Amsterdam	N=27	36.5%	N=46	62.2%	9.759	0.002*
IQ	99.93	10.47	103.55	10.77	3.605	0.060
Socio-economic status	11.26	2.02	12.07	2.52	4.522	0.035*
Follow-up interval (years)	5.92	0.60	5.86	0.68	0.258	0.613
Treatment prior to baseline=yes	N=52	70.3%	N=18	24.3%	31.335	<0.001*
ADHD type					8.677	0.070
Unaffected	N=6	8.1%	N=7	9.5%		
Inattentive	N=4	5.4%	N=6	8.1%		
Hyperactive	N=1	1.4%	N=2	2.7%		
Combined	N=55	74.3%	N=39	52.7%		
Subthreshold	N=8	10.8%	N=20	27.0%		
Comorbid problems #						
Anxiety/shyness	5.20	4.92	4.30	4.47	1.333	0.250
Perfectionism	3.85	4.24	3.55	3.55	0.214	0.644
Psychosomatic problems	3.45	3.33	2.80	3.16	1.445	0.231

Stat = Chi^2 for categorical variables, student-t for continuous variables. # scores on the anxiety/shyness scale, perfectionism scale, and psychosomatic problems scale of the parent- and teacher-rated Conners' questionnaires were used as a proxy of baseline comorbid problems. * = significant difference between treated and non-treated participants.

Stimulant treatment

Participants and parents provided written consent to request prescription records from their pharmacies. In addition, they reported lifetime history of psychoactive medication in a questionnaire at follow-up measurement. Pharmacy data covering the baseline-follow-up interval were available for 91% of participants with ADHD (n=135). Participants were classified as stimulant-treated if they had been prescribed any immediate or extended release methylphenidate preparations, or d-amphetamine preparations, between baseline and follow-up. When pharmacy transcripts were not available or incomplete (n=13), treatment history was derived from the questionnaire data. The questionnaire data was also used to determine stimulant treatment prior to baseline ("previously treated" or "stimulant-naïve") for all participants.

Outcome measures

Parent-rated numbers of hyperactivity-impulsivity and inattention symptoms were measured at baseline and follow-up using the respective DSM subscales of the CPRS (range 0:27). For participants using medication, parents rated behavior in the participant's non-medicated state. Four indicators of social-emotional functioning were derived from the SDQ for both time points: problems with emotion regulation, problems with peer relationships, conduct problems, and prosocial behavior (range 0-10).

In addition, six cognitive tests were administered at both baseline and follow-up. Three tasks measured motor control: Baseline Speed, in which participants were required to press a key upon unpredictable appearance of a stimulus; Pursuit, where participants followed a randomly moving target with the cursor as precisely as possible; and Tracking, in which participants were required to trace an invisible midline between an inner and an outer circle as precisely as possible. Two tasks measured timing: Time Estimation, where participants were asked to reproduce the duration of visually presented stimuli of different lengths (4, 8, 12, 16, and 20 seconds); and Motor Timing, in which participants were instructed to produce 1-second intervals as accurately as possible. Working memory was assessed in the backwards condition of the Digit Span test (WISC-III/WAIS-III), in which participants had to reproduce an increasingly long sequence of numbers in reverse order. For details, see Supplementary Table 1.

Statistical analyses

We used linear mixed effects models, predicting symptoms of hyperactivity/impulsivity and inattention, each of the four social-emotional outcomes, and performance on each cognitive test from time (baseline or follow-up), treatment ("stimulant-treated" or "not stimulant-treated" during the study phase), and time-by-treatment-interaction. The effect of interest is captured in the time-by-treatment interaction, which evaluated whether the outcome variables changed differently over time for the stimulant-treated group compared to the non-treated group. Baseline demographic/clinical between-group differences were included as covariates, as was a random intercept per family to account for dependencies among siblings. Multiple testing was accounted for by Bonferroni adjustment: alpha was divided by two for ADHD symptoms ($\alpha=0.05/2=0.025$), by four for social-emotional outcomes ($\alpha=0.012$), and by six for cognitive outcomes ($\alpha=0.008$).

Previous work by our group described changes over time in ADHD symptoms and cognitive functioning in participants with ADHD compared to typically developing participants (van Lieshout et al., 2016a; 2016b). Case-control differences are thus not the focus of the current study. Rather, the matched control group was used as a reference group for normative developmental changes. For visualization of estimated marginal means of all groups (stimulant-treated, not stimulant-treated, and control), the models described above were re-estimated across all participants with a fixed factor for group.

Sensitivity analyses were performed to test the robustness of our findings. With a relatively short wash-out time (48h), immediate withdrawal effects may have affected cognitive functioning in participants who received ongoing treatment at time of measurement. Therefore, analyses were repeated with an additional covariate encoding whether participants were actively being treated with stimulants within six months prior to assessment or not, and its interaction with the effect of interest (active treatment * time * treatment between baseline and follow-up). Second, all analyses were repeated with baseline age as an additional predictor, to address the wide age-range within our sample. Here, change over time in each outcome variable was predicted from age-by-treatment interaction, thus analyzing whether the effect of treatment on clinical/social-emotional/cognitive changes over time was different for participants of different ages.

RESULTS

Mean age of participants with ADHD was 11.1 years (SD=3.2) at baseline and 17.0 years (SD=3.3) at follow-up. Fifty-eight percent of participants was male.

Participants were diagnosed with ADHD or subthreshold ADHD at baseline (n=135, 91.2%) and/or at follow-up (n=132, 89.2%). Most participants reached diagnostic criteria at both times (n=119, 80.41%). Fifteen participants (10.1%) with subthreshold ADHD never met criteria for full ADHD diagnosis. At baseline, the majority of participants had combined type ADHD (n=94, 63.5%), while at follow-up the majority had either combined type (n=40, 27.0%) or inattentive type (n=51, 34.5%), with no differences between groups (Table 1). Within the stimulant-treated group, average cumulative stimulant dose between baseline and follow-up was 43336 mg, which equals 5.9 years of 20.1 mg per day. Forty participants (54.1%) had received active stimulant treatment within six months prior to follow-up assessment; the other participants had ceased stimulant treatment earlier. Participants in the stimulant-treated group had lower SES (p=0.035), were more likely to have received stimulant treatment prior to the initial assessment (Chi^2=31.335, p=0.001), and more likely to have received atomoxetine treatment between baseline and follow-up ($n_{OVERALL}$=16, 10.8%; $n_{TREATED}$=13, 17.6%; $n_{NON\text{-}TREATED}$=3, 4.1%; Chi^2=6.862, p=0.009). There was a site effect for stimulant treatment as well (Chi^2=9.759, p=0.002). Site, SES, and prior treatment were therefore added as covariates in all between-group comparisons. At baseline, the two treatment groups did not differ from each other with regard to any of the clinical or cognitive outcome measures.

There was a significant main effect of time on ADHD symptoms, as well as on two out of four social-emotional outcome measures (Table 2). Across all participants with ADHD, symptoms of hyperactivity/impulsivity and inattention, peer problems, and conduct problems improved between baseline and follow-up. There were no main effects of time on emotional problems or prosocial behavior. Improvement over time was also found for performance on all cognitive tasks: participants showed lower Baseline Speed variability, smaller deviations on the Tracking, Pursuit and Time Estimation tasks, and higher maximum Digit Span at follow-up compared to baseline.

There were no main effects of treatment group, and no time-by-treatment-group interaction effects on any of the outcome measures (Table 2, Figure 1 and 2). Thus, changes in ADHD symptoms, social-emotional and cognitive functioning over time were the same for participants who received stimulant treatment between baseline and follow-up and those who had not. Moreover, changes over time were the same for participants on active stimulant treatment at follow-up assessment and those who were not, suggesting no confounding by withdrawal effects. Finally, there were no significant interactions with age, suggesting that treatment effects were similar at different ages.

TABLE 2. Baseline and follow-up scores across treatment groups, and the effects of time, treatment, and time-by-treatment interaction.

	Baseline		Follow-up				
	EMM	SD	EMM	SD	p_{TIME}	$p_{TREATMENT}$	$P_{TIME*TREATMENT}$
Hyper/imp symptoms	14.22	5.95	11.83	6.73	<0.001*	0.212	0.188
Inattention symptoms	12.28	6.15	7.38	5.55	<0.001*	0.557	0.054
Emotional problems	2.98	3.00	2.82	3.08	0.736	0.577	0.707
Prosocial behavior	7.15	2.08	7.38	2.19	0.351	0.280	0.142
Peer problems	2.82	2.12	2.19	1.98	0.003*	0.382	0.424
Conduct problems	3.09	2.00	2.43	1.83	0.002*	0.238	0.906
Baseline Speed variability	172.37	103.89	90.29	50.35	<0.001*	0.513	0.672
Pursuit (inaccuracy)	6.44	3.74	3.87	0.76	<0.001*	0.609	0.320
Tracking (inaccuracy)	2.85	1.81	1.34	0.94	<0.001*	0.798	0.175
Motor Timing (inaccuracy)	203.11	95.10	148.83	51.48	<0.001*	0.449	0.341
Time Estimation (inaccuracy)	2.72	1.79	1.48	0.81	<0.001*	0.776	0.411
Digit Span	3.92	1.15	4.49	1.26	<0.001*	0.126	0.715

EMM=estimated mean score across participants with ADHD, adjusted for stimulant treatment prior to baseline measurement, site, and SES. *=p<0.012 or p<0.008.

DISCUSSION

Main findings

We investigated developmental changes in a broad spectrum of outcomes, including social-emotional and cognitive functioning, in stimulant-treated and not stimulant-treated individuals with ADHD who had been stringently matched on baseline characteristics and were non-medicated at both assessments. We found no evidence for any (beneficial or adverse) stimulant treatment effects persisting after stimulant treatment had temporarily been ceased. ADHD symptoms, peer problems, conduct problems, and performance on tests of motor control, timing, and working memory improved over time, but improvement occurred irrespective of treatment. Even at a lenient threshold for statistical significance, stimulant treatment was not associated with any of the outcomes.

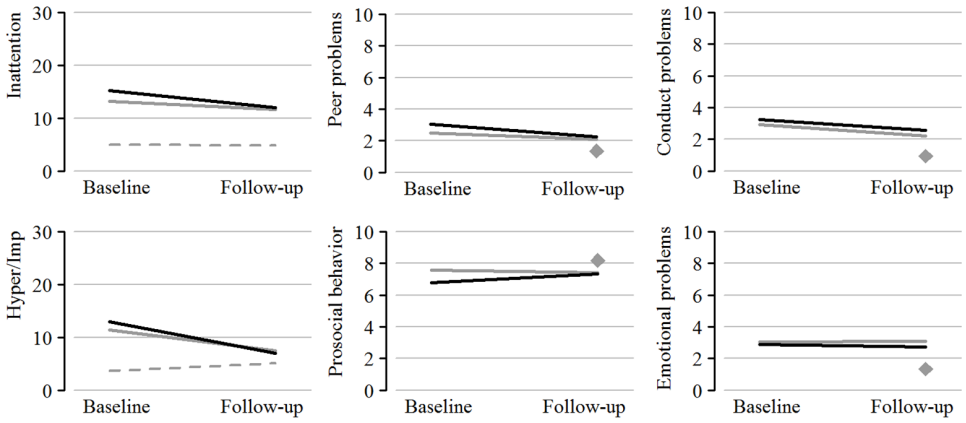

FIGURE 1. Change in ADHD symptoms and social-emotional outcome measures over ~6 years, for stimulant-treated (grey) and non-treated (black) participants with ADHD, and control participants (grey dashed), matched on baseline age, gender, and ADHD symptoms. Baseline social-emotional outcomes were not assessed for typically developing participants. The slopes of the two treatment groups did not differ for any outcome.

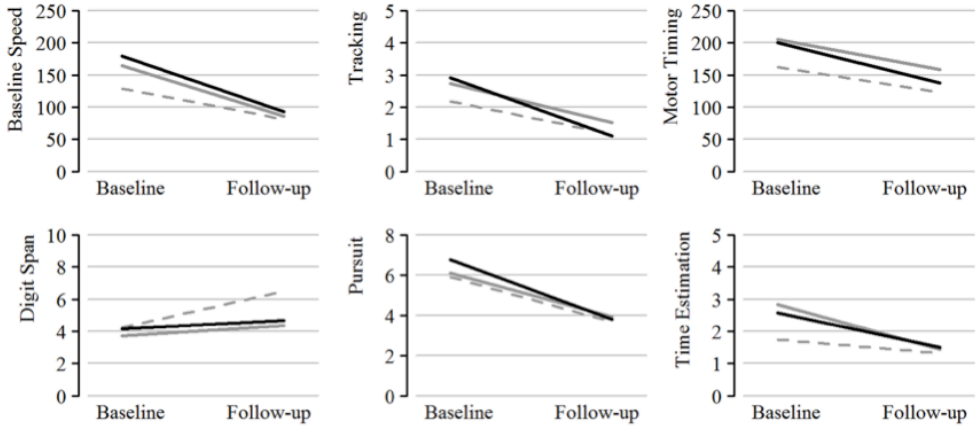

FIGURE 2. Change in cognitive test performance over ~6 years, for stimulant-treated (grey) and non-treated (black) participants with ADHD, and control participants (grey dashed), matched on baseline age, gender, and ADHD symptoms. The slopes of the two treatment groups did not differ for any outcome

Interpretation and previous studies

Our findings put into perspective previous studies reporting beneficial long-term effects of stimulant treatment. First, previous studies reporting long-term beneficial treatment effects oftentimes assessed outcomes when patients were on active treatment (Abikoff et al., 2004; Charach et al., 2004). Their findings may thus

represent either lasting effects of prior treatment, transient effects of ongoing treatment, or a combination of both. Our findings, in conjunction with reports of better outcome during phases of active stimulant treatment (Chang et al., 2016; Lichtenstein et al., 2012), suggest that previously reported long-term effects may be driven by ongoing transient effects rather than lasting effects. The absence of lasting treatment effects in our sample convenes with negative long-term findings of the MTA study, that have previously been attributed to self-selection during the observational phase (Molina et al., 2009; Swanson et al., 2007a). Our findings, however, underline the possibility that the theorized long-term effects may in fact not occur. At the same time, we wish to emphasize that beneficial long-term treatment effects have been found in outcomes that were not addressed here, such as the development of comorbid disorders later in life (Biederman et al., 2009).

Second, our findings are in line with a previous report of improved attention task performance after a one-year stimulant treatment episode even at drug-free status (Huang et al., 2012), which, in the absence of a reference group, could indicate either lasting beneficial treatment effects or improved cognitive performance at older age. In the current study, changes over time were the same in the treated and non-treated groups, suggesting that improvement over time is not related to treatment.

Third, several previous studies have reported more severe and/or more persistent ADHD in individuals who had received stimulant treatment during childhood, which could indicate either detrimental treatment effects or confounding-by-indication (Biederman et al., 2012; Molina et al., 2009; van Lieshout et al., 2016a). The current findings, free of confounding-by-indication due to stringent matching procedures and accounting for baseline measurements, provide no evidence of detrimental treatment effects.

Implications

The current findings are an important source to feed the scientific and public debate about pharmacological treatment for ADHD that has focused on long-term hazards and benefits. First, our findings emphasize that the course of ADHD symptoms and related outcomes are not altered by stimulant treatment. Previous work of our group showed that ADHD symptoms tend to decline but not disappear at later age (van Lieshout et al., 2016a). The current results add to these findings by showing that this conclusion holds for both stimulant-treated and non-treated individuals. Second, the absence of long-term treatment effects on clinical and cognitive outcomes may guide the interpretation of findings of structural brain changes associated with stimulant treatment (or the absence thereof). The evidence for normalized brain structure in children with ADHD who had received long-term

stimulant treatment is mixed (Schweren et al., 2015; Shaw et al., 2009; 2014). The absence of lasting treatment effects on a broad spectrum of clinical/behavioral outcomes emphasizes the importance of investigating behavioral correlates and clinical relevance of stimulant effects on the brain.

Strengths and limitations

This is the first longitudinal study investigating long-term treatment effects that included a non-treated ADHD and a typically developing sample and reported on a wide spectrum of clinical and cognitive outcomes. The average follow-up time of almost six years allowed the detection of effects emerging at later age, and captured the late adolescent/early adulthood phase that is often characterized by both clinical and normative developmental changes, which we were able to tease apart. Our rigorous one-to-one matching procedure allowed firm conclusions. Finally, extensive diagnostic assessments resulted in a well-characterized ADHD sample, and the availability of pharmacy records enabled highly reliable assessment of treatment history.

The current study had limitations as well. Treatment allocation was not random. We were able to rule out confounding-by-indication for all measured baseline variables, but not for non-measured potential between-group differences. Especially functional impairment and comorbidity could not satisfactorily be addressed. Propensity score adjustment would have been valuable in this regard, but was not feasible with the available data. Confounding may also have occurred during the study phase, e.g. behavioral treatment (not assessed) may have been more common in one group compared to the other. Second, findings regarding clinical outcomes furthermore rely on reports by parents, who were not blind to the participant´s treatment history or status. Third, the current design did not allow full investigation of treatment timing, since participants had often initiated treatment prior to the baseline measurement and/or continued treatment after the follow-up measurement. Treatment at different ages may be associated with different long-term consequences, although in our sample we found no indications of such effects.

SUPPLEMENTAL INFORMATION

TABLE S1. Neurocognitive tasks.

Task (aim)	Description	Performance measure	n
Baseline Speed (motor output in response to cue)	A white square appeared unpredictably (500-2500ms after response) on a screen, after which participants were required to press a key. Practiced and executed with the non-preferred hand, thereafter with the preferred hand.	Standard deviation of reaction times in ms averaged across both hands	78 (52.7%)
Pursuit (motor control with continuous adaptation)	Participants were required to 'catch' a randomly moving stimulus (asterisk, 10 mm/second) as precisely as possible by moving the cursor on top of the stimulus with the left hand.	Mean absolute distance in mm between target and cursor	81 (54.7%)
Tracking (motor control without continuous adaptation)	With the left hand, participants traced an invisible midline between an inner and outer circle presented on the screen (radius 7.5 and 8.5 cm, respectively), counterclockwise and as quickly and precisely as possible.	Mean absolute distance in mm between target (midline) and cursor	83 (56.1%)
Digit Span (working memory)	Participants were instructed to reproduce sequences of numbers, of increasing length, in reverse order.	Maximum accurately reproduced sequence length	111 (75.0%)
Time Estimation	Stimuli (4, 8, 12, 16, 20 seconds) were randomly presented by a lightbulb. Participants were required to reproduce stimulus length by pressing a button.	Absolute discrepancy between the response length and the stimulus length averaged across all 12-second trials.	83 (56.1%)
Motor Timing	Participants were instructed to produce a 1-second interval after a tone, as accurately as possible. Visual feedback was given, indicating whether the response was correct, too short or too long (defined by a dynamic tracking algorithm).	Median absolute deviation in ms from 1 second	88 (59.5%)

n = number of participants with ADHD who completed the task at baseline and at follow-up.