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Low, Ann-Marie Agerbo; le Sommer, Julijana; Vangkilde, Signe Allerup; Fagerlund, Birgitte; Glenthøj, Birte Yding; Sonuga-Barke, Edmund; Habekost, Thomas; Jepsen, Jens Richardt M.

REGULAR RESEARCH ARTICLE

Delay Aversion and Executive Functioning in Adults With Attention-Deficit/Hyperactivity Disorder: Before and After Stimulant Treatment

Ann-Marie Low, MSc, Julijana le Sommer, MD, Signe Vangkilde, PhD, Birgitte Fagerlund, PhD, Birte Glenthøj, PhD, Edmund Sonuga-Barke, PhD, Thomas Habekost, PhD, Jens Richardt Møllegaard Jepsen, PhD

Department of Psychology (Ms Low, Dr Vangkilde, Dr Fagerlund, and Dr Habekost), Center for Neuropsychiatric Schizophrenia Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Mental Health Centre Glostrup (Ms Low, Dr le Sommer, Dr Fagerlund, Dr Glenthøj, and Dr Jepsen), and Faculty of Health and Medical Sciences, Department of Clinical Medicine (Drs le Sommer and Glenthøj), University of Copenhagen, Copenhagen, Denmark; Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College, London, United Kingdom (Dr Sonuga-Barke); Child and Adolescent Mental Health Center, Mental Health Services, Copenhagen, Denmark (Dr Jepsen).

Correspondence: Ann-Marie Low, Department of Psychology, University of Copenhagen, Østre Farimagsgade 2A, 1353 Copenhagen K, Denmark (Ann-Marie.Low@psy.ku.dk).

Abstract

Background: Attention deficit hyperactivity disorder is a heterogeneous disorder, associated with deficits in motivation (e.g., delay aversion) and cognition. Methylphenidate is recommended as a first line treatment for attention deficit hyperactivity disorder symptoms, but little is known about its nonacute effects on motivational and cognitive deficits, particularly in adults with attention deficit hyperactivity disorder.
Methods: We utilized a prospective, non-randomized, non-blinded, 6-week follow-up design with 42 initially stimulant medication-naïve adult patients with moderate to severe attention deficit hyperactivity disorder, and 42 age- and parental education-matched healthy controls. Delay aversion and executive functioning were assessed with 2 questionnaires and 5 performance-based tests.
Results: At baseline, patients and controls differed significantly on performance-based measures (moderate to large effect sizes), and self-report of delay aversion and executive functioning (very large effect sizes). Treatment with methylphenidate medication (mean dose 65.54 mg/d, SD = 10.39) was not associated with improvements in performance-based measures of delay aversion and executive functioning compared to controls, although improvements in self-report executive functioning and delay aversion were found. Self-reported delay aversion was most consistently associated with ADHD symptomatology at baseline and after medication.
Conclusion: Methylphenidate treatment does not have an effect on performance-based measures of delay aversion and executive functioning, but may have significant effects on self-reported delay aversion and executive functioning. The latter finding should be interpreted cautiously, given the subjective nature of these measures and design limitations. Self-reported delay aversion is most consistently associated with attention deficit hyperactivity disorder symptomatology.

Significance Statement

Methylphenidate is effective at treating the symptoms of adults with ADHD. Acute studies have found that methylphenidate also has positive, significant effects on cognitive functioning. Here we demonstrated that adult ADHD was associated with both self-reported and objective measures of executive control and delay aversion. Furthermore, 6 weeks of methylphenidate treatment in adults was associated with improvements in both executive functioning and motivation, but these were limited only to subjective self-report and not found with objective tasks. Given the lack of blinding of treatment exposure, the association with subjective reports may be limited to changed perceptions rather than actual cognitive improvements.

Keywords: ADHD, motivation, executive functions, methylphenidate

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with a prevalence of around 2.5% in adults (Simon et al., 2009). Recently, dual pathway (Sonuga-Barke, 2002, 2003), and multiple pathway models (Sonuga-Barke et al., 2010) of ADHD have been proposed based on evidence of partially dissociable patterns of deficits in distinct neuropsychological domains in individuals with ADHD (e.g., Solanto et al., 2001; Sonuga-Barke et al., 2010; Coghill et al., 2014; Thorell et al., 2016; but see Lambek et al., 2017). Two domains thought to be particularly important are executive functioning (EF) and delay aversion (DA) (Sonuga-Barke, 2002, 2003).

DA is expressed as a number of different behaviors, theorized to be motivated by the desire to escape or avoid delay. It is postulated to be rooted in biologically based alterations in reward mechanisms, which, conditioned over time by the child's early experiences, result in delay experiences acquiring negative affective qualities. DA is expressed differently depending on whether delay can be avoided or not. In situations where delay can be reduced (i.e., where there is a choice), delay-averse individuals will tend to choose the more immediate option even if it means losing reward (Sonuga-Barke, 2002, 2003). Preference for "smaller sooner" over "larger later" rewards is regarded by many as the hallmark of DA (Bitsakou et al., 2009) and is supported by recent meta-analyses (Patros et al., 2016). However, where delay cannot be escaped, other activity and attention-based responses are required to reduce the perception of time in passing. For instance, on the Delay Frustration Test, sensitivity to interruption by unexpected and unavoidable periods of delay, where DA is expressed as an increase in frustration-related responding, was associated with higher levels of ADHD symptomatology in a nonclinical adult sample (Bitsakou et al., 2006). The Quick Delay Questionnaire, a self-report questionnaire concerning DA that includes items relating to both choice and nonchoice situations, differentiates between adults with ADHD and healthy controls (Clare et al., 2010) and to an extent clinical controls (Thorell et al., 2016).

EF deficits have long been associated with ADHD. Robust group differences between adults with ADHD and controls have been found in domains such as inhibitory control (Lijffijt et al., 2005; Mowinckel et al., 2015), working memory (Alderson et al., 2013), and planning/problem-solving (e.g., Chamberlain et al., 2011; Tucha et al., 2011). Questionnaires like the BRIEF-A (Roth et al., 2005) reveal robust self-reported EF deficits in ADHD. However, the overlap of performance-based tests and self-report assessments has been found to be nonsignificant (Biederman et al., 2008, 2015).

Cognitive Effects of Pharmacological Treatment in ADHD

Methylphenidate, a dopamine reuptake inhibitor, is recommended as a first line treatment for adult ADHD (Bushe et al., 2016). A recent meta-analysis reported positive, small- to medium-sized effects on response inhibition and working memory (Tamminga et al., 2016); however, evidence came mainly from acute administration studies. Positive effects of acute methylphenidate have also been found on adult ADHD planning skills (Chamberlain et al., 2011). Adult studies with active treatment periods of 1 to at least 10 weeks (Bouffard et al., 2003; Boonstra et al., 2005; Fallu et al., 2006; Tucha et al., 2006; Ni et al., 2013, 2016; Bron et al., 2014; Biederman et al., 2015; Skirrow et al., 2015; Goodman et al., 2017) and a single open-label study of up to 52 weeks (Ginsberg et al., 2012) have found positive effects on some aspects of attention; mixed findings with regards to working memory, response inhibition, and planning; and no effects on spatial span or forward digit span. Of 2 nonacute methylphenidate studies of delay-related behaviors, one adult study found positive effects of 2 weeks of methylphenidate on delay discounting (Crunelle et al., 2014), whereas no effects of 6 months of methylphenidate on DA was found in children (Morell and Expósito, 2017).

We undertook a prospective study to investigate the effect of 6 weeks of methylphenidate treatment on cognitive and motivational deficits in adults with ADHD. Our aims were first to examine whether methylphenidate treatment is associated with improvements in DA and EF and second, to investigate the association between these functions and ADHD symptomatology. We hypothesized that (1) at pretreatment, patients would demonstrate deficits in both DA and EF, and (2) after 6 weeks of medication adults with ADHD would, compared with controls, show significant improvements in DA and EF; further, that changes in symptoms would be associated with changes in DA and EF.

Methods

The project was undertaken in accordance with the Helsinki Declaration and approved by the Ethical Committee of the Capital Region Copenhagen (registration: H-15001438). Informed consent was obtained from all participants. Participants were compensated with a gift card/payment of €100 per testing day.

Participants

ADHD Patients

Stimulant medication-naïve adult patients with a primary diagnosis of disturbance of activity and attention (F90.0) or attention deficit disorder without hyperactivity (F98.8) according to ICD-10 criteria (World Health Organization, 1992) were recruited from the Adult ADHD Clinic at the Copenhagen University Hospital, Glostrup. Diagnosis at the ADHD clinic was undertaken in accordance with clinical guidelines (Sundhedsstyrelsen, 2015) and based on in-depth clinical interviews, including the DIVA 2.0 (Pettersson et al., 2015) interview with the patient, and wherever possible, a significant other; BRIEF-A questionnaire (Roth et al., 2005); the WHO Adult ADHD Self-Report Scale (ASRS) (Kessler et al., 2005); and additional testing (e.g., intelligence tests) as required. Inclusion criteria for all participants were age 18 to 45 years, legally competent, fluent in Danish, and fulfilled DSM-5 criteria of ADHD (ensured by checking patients' journal information, particularly DIVA 2.0 responses and clinical history). Exclusion criteria were: primary neurological or psychiatric diagnosis other than ADHD; confirmed diagnosis of other neurodevelopmental disorder including dyslexia; earlier diagnosis of severe depression; current suicidal tendencies; treatment with psychotropic drugs in the last 4 weeks, or with MAO-inhibitors in the last 2 weeks; treatment at any time with ADHD medication; substance abuse daily during the last 3 months and/or ongoing substance abuse; head injury ever with >5 minutes loss of consciousness; pregnancy; red-green color-blindness; need for "complex treatment"; and physical disease relevant for medication (e.g., cardiac disease). Absence of other primary psychiatric diagnoses was confirmed after completion of diagnostic screening interview, the Mini International Neuropsychiatric Interview 5.0 (MINI) (Sheehan et al., 1998). ADHD symptomatology was assessed with the ADHD Investigator Symptom Rating Scale (AISRS) (Spencer et al., 2010) and the ASRS (Kessler et al., 2005).

Healthy Controls

Controls were recruited from the internet site http://www.for-soegsperson.dk/ and matched at the group level on age, gender, and parental educational level. Exclusion criteria were: neurological, psychiatric, or neurodevelopmental diagnosis ever (mild/moderate depression/anxiety were not exclusion criteria); treatment with psychotropic drugs in the last 4 weeks, or with MAO-inhibitors in the last 2 weeks; treatment at any time with ADHD medication; substance abuse daily during the last 3 months and/or ongoing substance abuse; head injury ever with >5 minutes loss of consciousness; pregnancy; and red-green color-blindness. A total of 42 controls with a full baseline dataset were recruited, 38 of whom also completed follow-up testing. Controls undertook the same assessment as patients.

Design

The study was a prospective, nonrandomized, nonblinded, 6-week follow-up study; a placebo arm for patients was not included. A healthy control group was included at both assessment points in an attempt to control for retest effects. Patients' medication commenced as soon as possible after baseline testing; assessments of the participants were carried out on average 6.7 weeks (SD = 1.0) apart.

Medication Procedure

All patients were treated with a tool compound, methylphenidate, according to their clinical need (i.e., with individual titration). Treatment was initiated at a dose of 18 mg/d and increased in increments of 18 mg/d at 1-week intervals (minimum) until an optimal dose was reached with regards to ADHD symptoms and any side-effects. Judgement of medication effects and monitoring of side-effects were undertaken in weekly telephone consultations by the project psychiatrist (J.L.S.). A clinical appointment was undertaken 3 weeks after baseline, including a physical examination. A number of 37 of 38 patients were treated with Concerta, an extended-release tablet for once-a-day oral administration of methylphenidate. A stable "end-point" dosage was taken for at least 2 weeks before follow-up testing. Because of high sensitivity to methylphenidate, one patient was treated with the shorter duration methylphenidate, Medikenet CR. Final dosages of methylphenidate were 36 to 108 mg/d (M = 65.54 mg, SD = 10.39). All patients had positive tests for plasma methylphenidate at follow-up, showing medication compliance. Controls did not receive medication.

Test Procedure

All neuropsychological assessments were undertaken by a licensed specialist in neuropsychology (A.M.L.) or by master's-level students who received training and supervision from this specialist. After baseline testing, 3 patients were excluded, each for differing reasons, despite having valid baseline data (i.e., complex case requirements; uncorrected hearing loss preventing EEG investigations in a parallel part of the project; suspected allergic reaction to methylphenidate), and 1 dropped out, such that 38 of the 42 patients (90.5%) tested at baseline had follow-up data available for analysis.

Measures

Psychopathology

Psychopathology was assessed using 4 measures. The MINI 5.0 (Sheehan et al., 1998) is a short, structured interview for psychiatric disorders. The Clinical Global Impression scale (Guy, 1976) is a clinician rated, 7-point scale for assessment of ADHD illness severity. The ASRS (Kessler et al., 2005) is an 18-item, self-report screening scale of adult ADHD DSM-IV criterion A symptoms. Lastly, the AISRS (Spencer et al., 2010) is a semistructured interview scale with 18 items corresponding directly to the 18 DSM-IV symptoms of ADHD. Each of the 2 project clinicians rated the clinical interviews and rating scales independently, and consensus ratings were subsequently reached. In cases of disagreement, a third rater (last author J.R.M.J.) was consulted.

Neurocognition

Performance-Based Tests

The Delay Frustration Test (DeFT) is a test of delay frustration in the form of a computerized, simple mathematics test. During the test, unpredictable and unsignalled delay periods occur, either of 3 to 10 seconds duration on 8 "distractor trials" or 20 seconds on 8 "delay trials." Delay frustration is indexed as the mean total duration (MTD) of responding per second of delay on the delay trials and is the product of the average response frequency (i.e., number of responses per second) and the average duration of each response (i.e., total time of response per second). A novel measure was also calculated: the inter-response SD in each delay trial (DEFT-SD), measured in milliseconds.

The Digit Span sub-test (Wechsler, 2008) was used to assess auditory-verbal working memory. This is a composite score consisting of digit span forward, backward, and sequencing. Lastly, 3 tests from the Cambridge Neuropsychological Test Automated

Battery (Sahakian and Owen, 1992) were used. The Rapid Visual Processing task (RVP) is designed primarily to assess sustained attention capacity; here, we report the number of "False Alarms" (RVP-FA) as a measure of response inhibition (Fan et al., 2014; Chamari et al., 2016). Stockings of Cambridge (SOC) assesses spatial planning. Here, 3 parameters are reported: number of problems solved in the specified minimum number of moves (SOC-PS); the mean number of moves taken on the most difficult (5-move) problems; and mean initial thinking time on the most difficult problems (SOC-MIT). The spatial working memory task (SWM) (Robbins et al., 1994) is based on a self-ordered search task. Here, 2 parameters are reported; strategy utilization, the number of search sequences starting with a novel box in the difficult problems (SWM-strat); and the total errors committed in the course of the test (SWM-TE).

Questionnaires

The Quick Delay Questionnaire (QDQ) (Clare et al., 2010) is a 10-item questionnaire intended to tap 2 dimensions of delay-related behavior, each with 5-item scales: DA and delay discounting. BRIEF-A (Roth et al., 2005) is a 75-item self-report questionnaire concerning adults' views of their EF in their everyday environment. It consists of 9 subscales; here, the Working Memory, Inhibit, and Plan/ Organize subscales are reported, as these can be considered the equivalent of the EFs we investigated with performance-based measures.

Statistical Analyses

Data were analyzed with SPSS version 22. In case of missing data in the QDQ questionnaire (2 participants with ADHD and 2 healthy controls each missed 1 item), a score based on the rounded mean of the remaining scores for that subscale was imputed. All data were checked for skewness, normality, and outliers. Nonnormally distributed data were transformed (logarithmically or square root) to meet assumptions of normality and homogeneity of variance. Chi-square tests were used to assess differences between the patient and the control groups with regards to gender and parental education. Independent samples t tests were used to assess differences with regards to age, IQ, and ADHD symptomatology. Differences between the patient and the control groups at baseline with regards to neurocognition were analyzed by a MANOVA for questionnaires and performance-based assessments separately. In the case of a significant result, posthoc independent samples t tests were undertaken. Effect sizes were computed using Cohen's d ($d = M_1 - M_2/SD_{pooled}$). Differences in changes after treatment with medication between the patient and control groups were analyzed by a repeated-measures MANOVA for questionnaires and performance-based assessments separately. In the case of a significant finding, 2-way mixed ANOVAs were undertaken, with group as between-subjects factor and time as within-subjects factor, and effect sizes computed by partial eta squared (η_p^2). Further, within-group differences between baseline and follow-up performance were assessed by paired samples t tests. Spearman's rho was used for correlational analyses. All significance tests were conducted 2-tailed. Between-group analyses were re-run with estimated IQ as a covariate; any changes in significance as a result of these analyses are reported.

Results

Participant Characteristics

There were no significant differences between the patient and control groups on parental educational level, age, or gender.

However, the ADHD group had significantly lower estimated IQ and, as expected, significantly higher levels of ADHD symptomatology on both self-report and clinician-rated rating scales. On average, the patients were rated as having moderate to severe ADHD symptomatology on the Clinical Global Impression scale. A total of 47.6% of the patient group screened positive on the clinical interview (MINI) as having at least one comorbid psychiatric disorder (most commonly any anxiety disorder, $N = 18$, 33.3%). See Table 1 for an overview of sample characteristics.

Cognitive and Motivational Deficits Prior to Treatment

PA multivariate ANOVA showed a significant effect of group for both self-report measures ($V = .837$, $F_{(5,77)} = 79.046$, $P < .0005$) and performance-based tests ($V = .344$, $F_{(9,74)} = 4.311$, $P < .0005$). Patients reported greater levels of DA and EF difficulties on all questionnaire measures, with very large effect sizes (QDQ DA $t(82) = 10.186$, $P < .0005$; delay discounting $t(82) = 9.201$, $P < .0005$; BRIEF-A inhibit scale $t(81) = 12.486$, $P < .0005$; BRIEF-A working memory scale $t(81) = 16.740$, $P < .0005$; and BRIEF-A planning/ organization scale $t(81) = 15.372$, $P < .0005$; see Table 2 for details).

Individuals with ADHD also demonstrated significant deficits on tests of cognitive functioning, with the exception of the standard measure of delay frustration (DeFT-MTD: $t(82) = -1.397$, $P = .166$) and the mean initial thinking time on the SOC (SOC-MIT: $t(82) = 1.437$, $P = .155$). Deficits were of large effect sizes for SWM total errors and digit span (SWM-TE $t(82) = 4.533$, $P < .0005$; digit span $t(82) = 5.022$, $P < .0005$). They were of moderate to large effect size for false alarms on the RVP, SWM strategy, and SOC number of problems solved (RVP-FA: $t(82) = 2.688$, $P = .009$; SWM-strat: $t(82) = 3.415$, $P = .001$; SOC-PS $t(82) = 2.468$, $P = .016$) and of small to moderate sizes for the novel measure of the DeFT (DEFT-SD: $t(82) = 2.016$, $P = .047$). Finally, mean moves to solve 5-move problems on the SOC just missed significance (SOC-MM $t(82) = 1.983$, $P = .051$).

When analyses were re-run with IQ as a covariate, significance levels for differences between the groups were reduced and just missed significance for SWM-strat ($P = .053$) and became clearly insignificant for DEFT-SD, RVP-FA, SOC-PS, and SOC-MM ($P > .19$).

Exploratory Associations Between ADHD Symptomatology and Neurocognition

At baseline, in the patient group, 10 of 56 correlations between neurocognitive measures and ADHD symptomatology were significant, all in the small to medium ranges. The QDQ subscales were significantly associated with all ADHD symptomatology ratings (6 of 8 correlations), while only 1 of 12 correlations between BRIEF-A subscales and ADHD symptomatology was significant. Of the performance-based measures, 3 of 36 correlations with ADHD symptomatology were significant. See Table 3 for details.

Changes in Cognition After Methylphenidate Treatment

Repeated-measures MANOVA showed a significant group by time interaction for self-report measures ($V = .242$, $F_{(1,73)} = 23.294$, $P < .0005$) but not for performance-based tests ($V = .009$, $F_{(1,74)} = .669$, $P = .416$). Thus, 2-way mixed ANOVAs were undertaken only for the questionnaire measures. Significant interactions were seen for all questionnaire measures (QDQ DA $F_{(1,74)} = 10.854$, $P = .002$ and QDQ delay discounting $F_{(1,74)} = 6.937$, $P = .010$; BRIEF-A inhibit

Table 1. Demographic and Clinical Characteristics of Adults With ADHD and Control Participants at Baseline

	Patients (n = 42)	Controls (n = 42)	P
Ages, y (SD)	26.9 (7.38)	26.7 (5.6)	n.s.
No. (%) female	16 (34.0%)	18 (42.9%)	n.s.
Parental education (1–3) (SD)[a]	1.93 (.52)	1.90 (.53)	n.s.
Inter-session interval, weeks (SD)	6.7 (1.0)	6.7 (0.8)	n.s.
Estimated IQ (SD)[b]	92.1 (13.1)	103.6 (10.88)	<.0005
ADHD symptomatology	51.7 (9.5)	21.0 (9.0)	<.0005
ASRS (SD)[a]	38.6 (7.6)	7.5 (5.2)	<.0005
AISRS (SD)[c]	4.62 (0.69)	1.14 (0.42)	<.0005
Clinical Global Impression scale (SD)			
No. (%) psychiatric comorbidities (MINI)	22 (52.4%)	41 (97.6%)	-
0	20 (47.6%)	1 (2.4%)	-
≥1	14 (33.3%)	0 (0.0%)	-
≥2			

Abbreviations: ASRS, Adult ADHD Self-Report Scale; AISRS, Adult ADHD Investigator Symptom Rating Scale; MINI, The Mini International Neuropsychiatric Interview; -, no statistical analysis undertaken.

Parental education was rated on a scale of 1 to 3 for the parent with the highest education, 1 indicates higher education.

The most common psychiatric disorders were: any anxiety disorder, n = 18; suicidality, n = 8 (no current suicidal ideation); dissocial personality disorder, n = 8; depression, n = 4. One control participant screened positive for depression.

[a]One missing data point.

[b]Range of estimated IQ at baseline for patients was 68 to 123; only 1 patient had an estimated IQ <70.

[c]The scale was used as an additional measure after commencement of the study, and there are missing data points for the first participants (baseline, n = 9; follow-up, n = 4).

$F_{(1,74)} = 14.192$, $P < .0005$; BRIEF-A working memory $F_{(1,74)} = 15.011$, $P < .0005$; and BRIEF-A planning and organization $F_{(1,74)} = 16.888$, $P < .0005$. See Table 2 for details.

Posthoc within-group analyses indicated that, compared with baseline, patients at follow-up reported significantly fewer difficulties on all questionnaire measures (all $P < .0005$). On cognitive tests, they improved significantly on SWM-TE ($t(37) = 3.046$, $P < .004$), digit span ($t(37) = 2.159$, $P = .037$), and SOC-PS ($t(37) = 2.058$, $P = .047$). Changes just missed significance for SWM-strat ($t(37) = 1.804$, $P = .052$) and were insignificant for RVP-FA, DEFT-SD, DEFT-MTD, SOC-MIT, and SOC-MM (all $P > .10$).

Associations Between Changes in ADHD Symptomatology and Neurocognition

Ratings of ADHD symptomatology decreased significantly after methylphenidate treatment in the patient group compared with the control group (all $P < .004$; see Table 2). Correlational analyses were undertaken between changes in ADHD symptomatology scores and the neurocognitive measures that had shown a significant change when controlling for retest effects in the patient group. Changes in QDQ scales showed significant, moderate correlations (all r_s .434 to .663) with changes in all ADHD symptom scales/subscales. Of the BRIEF-A subscales, Working Memory and Planning/Organization together showed 3 significant associations with a symptomatology measure (self-rated ADHD symptoms and clinician rated inattention symptoms; r_s .365 to .450). See Table 4 for details.

Discussion

The primary purpose of this study was to investigate whether DA and EF improved after 6 weeks of methylphenidate treatment in a sample of initially stimulant medication-naïve adults with ADHD. When controlling for retest effects, we found no significant improvements in the ADHD group on any performance-based test of DA or EF; in contrast, patients reported significant improvements in DA and EF as assessed with self-report questionnaires.

Performance-Based Measures

The lack of improvement on performance-based measures is initially surprising, given significant, positive effects of methylphenidate on response inhibition, working memory, and planning/problem-solving in adults with ADHD reported in recent meta-analyses/reviews (Chamberlain et al., 2011; Tamminga et al., 2016). However, these mainly include acute studies, whereas the findings of prospective studies investigating the effect of at least 1 week of methylphenidate treatment in these cognitive functions in adults with ADHD are mixed. This could stem from a number of methodological differences, such as whether patients were initially stimulant medication-naïve, final average dosage of medication, titration schedule, degree and type of comorbidity, and which measures were utilized to measure (the same) neurocognitive function. Of note, a study that utilized the same measure of response inhibition as this study (RVP-FA) did not find significant effects of methylphenidate (Ni et al., 2013); studies that utilized other measures have found a positive effect. Thus, for this particular measure, test insensitivity for (small) treatment effects may have been a factor.

Possibly the most important explanatory factor of previous mixed results is the extent to which retest effects were controlled for. Thus, for working memory and planning, 3 previous studies have reported significant, positive effects but were all uncontrolled (Fallu et al., 2006; Ginsberg et al., 2012; Ni et al., 2013). Controlled children's studies have found mixed effects of methylphenidate treatment for these functions (e.g., Coghill et al., 2007; Cristiana et al., 2017; Kortekaas-Rijlaarsdam et al., 2017; Morell and Expósito, 2017). Two randomized control trial (RCT) studies indicate positive, significant effects of methylphenidate for measures of response inhibition (Bouffard et al., 2003; Boonstra et al., 2005), but these and 2 additional studies (Ni et al., 2013; Bron et al., 2014) also report nonsignificant findings.

Table 2. Cognitive Functioning of Adults With ADHD and Control Participants at Baseline and Follow-Up

Measure	Baseline			Follow-up			Group x session interaction
	Patients M (SD)	Controls M (SD)	D	Patients M (SD)	Controls M (SD)	d	η_p^2
QDQ DA	3.34 (.76)	1.88 (.53)	2.23***	2.54 (.75)	1.59 (.50)	1.49***	.128**
QDQ DDis	3.39 (.77)	2.05 (.53)	2.03***	2.69 (.72)	1.82 (.60)	1.31***	.086*
BRIEF-A – inhib	17.71 (3.62)	9.74 (1.83)	2.78***	14.18 (3.70)	8.89 (1.27)	1.91***	.157*
BRIEF-A – WM	19.56 (3.03)	10.19 (1.97)	3.67***	15.42 (4.09)	9.32 (1.34)	2.00***	.115*
BRIEF-A – plan	22.12 (3.02)	12.57 (2.63)	3.37***	17.66 (4.30)	11.18 (1.20)	2.05***	.185***
DEFT - MTD (ms)	105 (145)	147 (194)	-	74 (103)	226 (332)	- .61*	-
DEFT - SD (ms)	2083 (1616)	1460 (1049)	.46*	2148 (1593)	1408 (1347)	.50*	-
RVP - FA	2.69 (3.09)	1.31 (1.24)	.59**	1.66 (1.85)	0.87 (1.19)	.51*	-
SWM strategy	30.64 (5.67)	26.38 (5.77)	.74*	28.03 (6.29)	23.82 (5.25)	.73**	-
SWM total error	20.52 (17.00)	7.71 (7.89)	.97***	13.61 (14.92)	4.79 (6.48)	.77***	-
Digit span	23.00 (3.69)	27.12 (3.83)	1.09***	24.47 (4.37)	28.74 (4.55)	.96***	-
SOC – MIT	7849 (6037)	9843 (6664)	-	9476 (8986)	9945 (5375)	-	-
SOC – PS	9.12 (1.70)	10.02 (1.66)	.53*	9.76 (1.73)	10.74 (1.45)	.61**	-
SOC – MM	6.38 (1.28)	5.87 (1.01)	·	6.11 (1.25)	5.61 (0.94)	.45*	-
ASRS	51.7 (9.5)	21.0 (9.0)	3.32***	32.9 (12.4)	16.3 (9.6)	1.50***	.334***
AISRS	38.6 (7.6)	7.5 (5.2)	4.78***	18.3 (9.3)	4.70 (4.9)	1.83***	.130**

Abbreviations: AISRS, Adult ADHD Investigator Symptom Rating Scale; ASRS, Adult ADHD Self-Report Scale; d, Cohen's d; DEFT, Delay Frustration Test; DaV, Delay Aversion; DDis, Delay Discounting; inhib, inhibit subscale; MTD, Mean Total duration of pressing per second of delay; ηp2, partial eta squared; plan, planning/organization subscale; QDQ, Quick Delay Questionnaire; RVP-FA, no. of false alarms; SWM strategy, number of search sequences starting with a novel box in the difficult problems; SWM-total error, total number of errors committed; SOC-MIT, mean initial thinking time on 5-move tasks; SOC-PS; problems solved in the specified minimum number of moves; SOC-MM, mean number of moves to solve 5-move tasks; WM, Working Memory subscale.

* P < .05 ** P < .01 *** P < .001.

Lastly, our findings regarding the performance-based test of delay frustration are novel for an adult population but in line with one randomized, open controlled child study (Morell and Expósito, 2017).

The present study included a healthy control group, but interpretation of our null findings with respect to performance-based measures should be considered in light of a number of methodological weaknesses. Our sample was relatively small, thus increasing likelihood of a type I error, and one-half of the patients screened positive for a secondary diagnosis other than ADHD (most commonly an affective disorder). However, dominating psychiatric comorbidities (e.g., substance use disorders, severe depression) known to affect cognitive functioning were exclusion criteria in this study. Few prospective studies have investigated the impact of comorbid affective disorders on the effect of methylphenidate treatment on neurocognition, but comorbid depression may not impact methylphenidate effects (Riordan et al., 1999). Further, we investigated a relatively narrow range of neurocognitive functions with only 1 or 2 tests of each. A broader battery of tests for specific neurocognitive functions and/or investigating a wider range of functions may have increased sensitivity to any effect of methylphenidate. Alternatively, the stability of these specific neurocognitive deficits, in conjunction with reduced ADHD symptomatology with medication, may be an indication of state independence (Gottesman and Gould, 2003; Braff et al., 2007), which could support previous evidence of cognitive biomarkers or endophenotypes in ADHD (Pironti et al., 2014).

Self-Report Measures
There are to our knowledge no former studies of changes in self-reported DA after stimulant treatment. Our findings of medium- or large-sized effects for self-reported working memory,

inhibition, and planning/organization extend previous findings of changes in self-reported EF after stimulant medication treatment, where retest effects were not controlled for (Biederman et al., 2015). While our use of a healthy control group allows some control for retest effects, a full RCT design would have allowed control of potential placebo effects and offered some degree of "structural equivalence" between our groups (Kabisch et al., 2011). This in turn would have allowed stronger conclusions concerning the effect of treatment on self-report measures, which may be more prone to reporter effects that performance-based measures (Sonuga-Barke et al., 2008). However, a previous RCT found a positive, significant effect of methylphenidate on the General Executive Index score from the BRIEF-A (Goodman et al., 2017). This supports the hypothesis that changes in self-reported neurocognition associated with methylphenidate treatment are not solely the result of nonoptimal methodology.

The difference in findings according to type of assessment, notwithstanding the limitations of our design, is potentially interesting. It is now fairly well accepted that there is little overlap between performance-based and self-report measures of cognition (Biederman et al., 2008; Toplak et al., 2013; Fuermaier et al., 2015). While performance-based tasks are generally described as more objective and self-report as more ecologically valid (e.g., Roth et al., 2005), this dissociation may reflect that measures assess different underlying mental constructs and provide important and nonredundant information (Toplak et al., 2013). This has been argued to be the case especially for DA (Thorell et al., 2016).

Group Difference in EF and DA at Baseline

Pretreatment, stimulant medication-naïve ADHD patients reported very large, significant impairments in DA behaviors,

Table 3. Correlations Between Cognitive and Motivational Measures and ADHD Symptomatology at Baseline for Patients

ADHD Symptom-atology		QDQ-av	QDQ-dis	BRIEF inhib	BRIEFWM	BRIEFPO	DEFT-MTD	DEFT-SD	RVP-Fa	SWM-strat	SWM-TE	Digit span	SOC- PS	SOC-MIT5	SOC-MM5
											Cognitive and motivational measures				
ASRS	r_s	.365*	.264	.090	-.027	.117	.150	-.134	.197	.119	-.037	.001	.026	-.135	-.182
	n	41	41	40	40	40	41	41	41	41	41	41	41	41	41
AISRS	r_s	.386*	.460**	.215	-.024	-.002	-.060	.095	.132	.281	.320	-.019	-.216	-.438**	.026
	n	37	37	36	36	36	37	37	37	37	37	37	37	37	37
ASIRS inn	r_s	.192	.341*	-.163	-.002	.199	-.076	.101	.134	.334*	.323	-.056	-.284	-.437**	.054
	n	37	37	36	36	36	37	37	37	37	37	37	37	37	37
ASIRS hyp	r_s	.434**	.368*	.450**	-.006	-.197	.030	-.012	-.004	.089	.177	.036	-.110	-.222	-.025
	n	37	37	36	36	36	37	37	37	37	37	37	37	37	37

Abbreviation: hyp, hyperactive; inn, inattentive; r_s, correlation coefficient. For other abbreviations, please refer to Tables 1 and 2. Shading indicates significant correlations. n differs due to missing data for ASRS and AISRS as described in Table 1; BRIEF-A is missing for 1 participant.

* P <.05 ** P <.01 *** P <.001.

working memory, response inhibition, and planning. They also performed significantly worse on all performance-based tests of these domains, generally with moderate to large effect sizes. We failed, however, to find a significant between-group difference on the original measure of our performance-based test of DA (DEFT-MTD). Nonetheless, clinically it appeared that at least some of our patients responded to the unsignaled delay periods of the Delay Frustration Test to a greater extent than controls (e.g., with heightened levels of expressed frustration and physical activity). These types of responses have been hypothesized to result from underlying DA (Sonuga-Barke, 1994, 2005), which may reflect an attempt to attentionally disengage from the delay situation (Scime and Norvilitis, 2006; Cheyne et al., 2009). We aimed to index this possible disengagement with a novel measure, the SD of inter-response interval (DEFT-SD), and found significant group differences, which is the first time this has been demonstrated in an adult clinical sample.

Some of the specific neurocognitive deficits observed at baseline (i.e., response inhibition, strategy formation, planning, and DA) may have been partly mediated through lower IQ. There is disagreement as to whether studies of cognition in ADHD should control for IQ (e.g., Bridgett and Walker, 2006; Dennis et al., 2009). Our sample of patients had a mean estimated IQ of 92.1 (SD = 13.1), lower than could be expected from a meta-analysis indicating an average decrement of 3 IQ points in adults with ADHD (Bridgett and Walker, 2006). This may partly reflect that we did not have exclusion criteria related to IQ and may lend weight to the argument that results should be presented with and without controlling for IQ (Bridgett and Walker, 2006) in this particular study.

Association Between Neurocognition and ADHD Symptomatology

Very few significant associations between performance-based neurocognitive measures and ADHD symptoms in patients at baseline were observed, even in exploratory analyses. These findings are in line with the few studies of stimulant medication-naïve individuals with ADHD that report these associations (e.g., Boonstra et al., 2005; Coghill et al., 2007; Bron et al., 2014). Further, these studies and the present study report a relative lack of association between changes in cognition and ADHD symptomatology after methylphenidate treatment. Together, these findings suggest a weak relationship between cognition and ADHD symptomatology. In particular, while methylphenidate clearly reduces severity of ADHD symptoms, it improves neurocognitive deficits to a lesser extent (e.g., Coghill et al., 2014). A possible explanation for these findings could again be that at least some cognitive functions are demonstrating state independence. Alternatively, it may be that differential dose-response relationships exist for cognition and ADHD symptoms, respectively (Hale et al., 2011).

Exploratory analyses between self-report measures and ADHD symptomatology (both self-report and clinician-rated) showed a number of significant associations, most consistently with delay-related behaviors. This was the case both at baseline and with regards to changes after methylphenidate treatment. In contrast, very few associations between self-reported EF and ADHD symptomatology were significant. Pretreatment findings are in line with previous studies (Biederman et al., 2008, 2015). However, Biederman and colleagues (Biederman et al., 2008) also reported that improvements in self-reported EFs closely tracked improvement for ADHD symptoms after 6 weeks of treatment (formal associations between these variables were not reported).

Table 4. Correlations in the Patient Group Between Changes in ADHD Symptoms and Changes in QDQ and BRIEF-A Subscales

ADHD symptomatology		Self-report measures				
		Δ BRIEF-A inhib	Δ BRIEF-A WM	Δ BRIEF-A PO	Δ QDQ dis	Δ QDQav
Δ ASRS	r_s	.298	.251	.365*	.663***	.497**
	n	36	36	36	37	37
Δ ASIRStot	r_s	.282	.209	.281	.395*	.506**
	n	32	32	32	33	33
Δ ASIRSInn	r_s	.167	.450*	.442*	.295	.489**
	n	32	32	32	33	33
Δ ASIRShyp	r_s	.189	-.077	-.006	.330	.346*
	n	32	32	32	33	33

Abbreviations: Δ, change; AISRS Inn, AISRS Inattentive scale; AISRShyp, AISRS hyperactivity scale; AISRStot, adult ADHD investigator symptom rating scale; ASRS, Adult ADHD Self-Report Scale; BRIEF-A Imp, response inhibit subscale; BRIEF-A WM, Working Memory subscale; PO, planning/organization subscale; QDQ dis, Quick Delay Questionnaire, Delay Discounting scale; QDQav, QDQ delay aversion scale; r_s, Spearman's correlation. Shading indicates significant associations. n differs due to missing data for ASRS and AISRS as described in Table 1; BRIEF-A is missing for 1 participant.
* $P < .05$ ** $P < .01$ *** $P < .001$ (2-tailed).

Differences in study design/statistical methods may partly explain our differing findings.

This study has several limitations. Most importantly, a placebo condition was not included, and clinicians were not blinded to participant or medication status, thus weakening conclusions concerning whether self-reported changes after methylphenidate treatment can be regarded as relating to real changes in cognitive function rather than merely perceptions of improved functioning influenced by knowledge of treatment exposure. Further, we screened for psychiatric comorbidity using an instrument (MINI) that characterises disorder in binary terms rather than an instrument allowing dimensional ratings, and thus we could not investigate the effect of subthreshold symptoms of, for example, affectivity (Karalunas et al., 2014). In light of these limitations, interpretations must be cautious. Nonetheless, our findings indicate that stimulant medication-naïve adults with ADHD exhibited deficits in cognitive tests and self-reports of EF and DA. After 6 weeks of methylphenidate treatment, no improvements were seen in the ADHD group on performance-based measures of these functions; in contrast, patients reported significant improvements in these same functions. Associations between neurocognitive measures and ADHD symptomatology were found most consistently for self-reported DA.

Statement of Interest

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