CHAPTER 2

OROS-methylphenidate efficacy on specific executive functioning deficits in adults with ADHD. A randomized, placebo-controlled cross-over study


Published in: European Neuropsychopharmacology 2014; 24(4):519-528.
ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is linked to impaired executive functioning (EF). This is the first study to objectively investigate the effects of a long-acting methylphenidate on neurocognitive test performance of adults with ADHD. Twenty-two adults with ADHD participated in a 6-weeks study examining the effect of osmotic-release oral system methylphenidate (OROS-mph) on continuous performance tests (CPTs; objective measures), and on the self-reported ADHD rating scale (subjective measure) using a randomized, double-blind, placebo-controlled cross-over design. OROS-mph significantly improved reaction time variability (RTV), commission errors (CE) and d-prime (DP) as compared to baseline (Cohen’s d>0.50), but did not affect hit reaction time (HRT) or omission errors (OE). Compared to placebo, OROS-mph only significantly influenced RTV on one of two CPTs (p<.050). Linear regression analyses showed predictive ability of more beneficial OROS-mph effects in ADHD patients with higher EF severity (RTV: β=0.670, t=2.097, p=.042; omission errors (OE): β=-0.098, t=-4.759, p<.001), and with more severe ADHD symptoms (RTV: F=6.363, p=.019; HRT: F=3.914, p=.061). Side effects rates were substantially but non-significantly greater for OROS-mph compared to placebo (77% vs. 46%, p=.063). OROS-mph effects indicated RTV as the most sensitive parameter for measuring both neuropsychological and behavioral deficits in adults with ADHD. These findings suggest RTV as an endophenotypic parameter for ADHD symptomatology, and propose CPTs as an objective method for monitoring methylphenidate titration.
INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is characterized by a childhood onset and lifelong persistence of symptoms of inattention, hyperactivity and/or impulsivity [78], and is prevalent in 3.4% of adults [11]. ADHD is thought to be caused by dysregulated catecholaminergic neural circuits, which regulate the amounts of dopamine and epinephrine available in the frontal lobe [79]. Minor changes in the supply of catecholamines have marked effects on prefrontal cortical balance, which mediates the neural networks of executive functions (EF) [80]. EFs manage and control behavior, especially in the efficiency of goal-directed behavior. Individuals with ADHD have impaired neurocognitive functions in the EF areas of (sustained) attention, effortful control, processing speed, and fluency when compared to those without ADHD [19, 81-83]. Although EF deficits are highly heterogeneous in ADHD on a group level and present in only 40% of patients [16, 17], they are heritable [84] and individually stable over the course of development [85]. Thereby, neurocognitive deficits furnish accurate and objective descriptions of phenotypes for psychiatric disorders [84], which are almost directly linked to behavior in ADHD [86]. The severity of EF deficits has even been linked to ADHD severity [87].

Stimulant medications such as methylphenidate are the pharmacological treatment of choice for ADHD [61]. In clinical practice among adults, methylphenidate preparations with a long-acting release profile (osmotic-release oral system; OROS-mph) are preferred over immediate-release methylphenidate (IR-mph), primarily because of the longer duration of action [88]. Irrespective of the type of release profile, ADHD patients have difficulties evaluating the methylphenidate efficacy on ADHD symptoms during and after treatment [89]. Largely depending on subjective patient reports may therefore hinder reliable titration of medication, and quantification of clinical improvement using objective measures is needed.

Objective continuous performance tests (CPTs) measure executive functioning, and are able to discriminate ADHD patients from normal controls [90, 91], and IR-mph responders from non-responders in both children and adults with ADHD [19, 92]. Visually, methylphenidate increases frontal and striatal metabolism on functional neuroimaging scans (fMRI) [93], and neurocognitively, it normalizes EF deficits in the areas of attention, vigilance, response speed, and inhibition in children [92, 94] as well as adults with ADHD [20, 91]. The few studies focusing on CPT performance in adults with ADHD only tested IR-mph effects [19, 91], used
very low IR-mph doses [95], or investigated a limited range of CPT parameters [96]. As yet, neurocognitive research studying the effects of long-acting methylphenidate in an adult population with ADHD has not been conducted, nor have specific CPT parameters been linked to the ADHD endophenotype.

This study is the first to investigate the efficacy of OROS-mph on specific EF deficits among adults with ADHD. From IR-mph results and studies among children with ADHD, OROS-mph is expected to ameliorate EF deficits in adults with ADHD, and to show variable efficacy results for specific CPT parameters [20, 91, 94]. Hereby, we aim at (1) extending the current understanding of using specific, objective CPT parameters as indicators of the neuropsychological underpinnings of the ADHD endophenotype; and (2) evaluating CPTs as an instrument for monitoring OROS-mph titration in adult ADHD patients.

EXPERIMENTAL PROCEDURES

Study design

Figure 1 presents the flow-chart of this 6-weeks randomized, double blind, placebo-controlled, cross-over trial. Simple randomization was applied for medication order as well as for CPT order, without any restrictions for equality of group sizes.

Participants

We recruited drug-naive patients between 18 and 55 years of age who were diagnosed with the combined subtype of ADHD, from the PsyQ outpatient Adult ADHD clinic in The Hague, The Netherlands. Diagnostic assessment of ADHD was conducted by a trained psychologist using the Diagnostic Interview for ADHD in adults, second edition (DIVA 2.0; [97]). ADHD diagnoses were based on having at least 6 of 9 DSM-IV symptoms of inattention and hyperactivity/impulsivity in childhood, a chronic persisting course of symptoms and impairment, and having at least 4 of 9 DSM-IV symptoms of inattention and hyperactivity/impulsivity in adulthood [98]. Exclusion criteria were: severe comorbid psychiatric disorders at time of the screening interview (using the Structured Clinical Interview for DSM disorders; SCID [99]), treatment with stimulants, antipsychotics, clonidine, benzodiazepines, or beta-blockers within one month prior to study participation or any medication that could influence the CPT performance (i.e. TCA or SSRI), any cognitive disorder like dementia or amnesic disorder, mental retardation, or being pregnant or nursing.
FIGURE 1. Flowchart of the 6-weeks procedure and randomizations of our double-blind, placebo-controlled cross-over study, with every subject receiving both treatments. Note. N=total sample size; n=group size; SCID=Structured Clinical Interview for DSM disorders; CPTs=Continuous Performance Tests.
Medical-ethical approval has been obtained (METiGG; #7208; CCMO; #NL16911.097.07). Public trial registration #ISRCTN52392534.

Treatment
An independent pharmaceutical company manufactured the visually identical over-encapsulated tablets containing either OROS-mph or placebo. OROS-mph treatment was initiated with a once daily dose of 36 mg and continued with an increment of 36 mg after 7 days, resulting in a total once daily dose of 72 mg for all patients in weeks 3 and 6. Standard titration rules for children proclaim increments of 18 mg per 7 days, but titration with 36 mg at once is clinically well tolerated in adult patients. This study evaluated the effect of 72 mg OROS-mph following Newcorn et al. [100]. All subjects took the study medication at 8 AM for optimal methylphenidate plasma concentrations during the CPT task, which was conducted at 9:30 AM [101]. Medication was administered at visits 1, 2, 4 and 5 (Figure 1). Adverse medication effects were scored on the Side Effects Rating Scale [102], comprising the presence of the 14 most common side effects of methylphenidate according to the European Medicines Agency’s summary of product characteristics [103]. Adherence to medication intake was tracked using the Adherence Questionnaire [104].

Outcomes
Objective response
Two widely used and commercially available, computerized CPTs were administered for measuring executive functioning. One is the Conners’ Continuous Performance Test (C-CPT-II Version 5; [105]), a 14-minutes task aiming to assess attention disorders and neurological functioning. Subjects are required to press the space bar as fast as possible each time any letter, except the letter “X” (in 10% of cases), appears on the screen. The task is divided into six blocks of 20 stimuli (letter presentations) each, with stimuli displayed for 250 milliseconds and varying inter-stimulus intervals (ISIs) of 1, 2, and 4 seconds. The other one is the 21.6-minute visual part of the Test of Variables of Attention (TOVA; [106]), where subjects press a micro switch as fast as possible each time a small white square appears in the upper half of a large black square (a ‘target’) on the screen. There are two conditions: a stimulus-infrequent condition with few targets (22.5% of all stimuli) and thus a low response demand, which aims at measuring attention, and a stimulus-frequent condition with many targets (77.5% of all stimuli) and a high response demand, which aims at measuring inhibition. Stimuli are displayed for 100 milliseconds at 2-second intervals.
each. Both CPTs have a high internal consistency ($r \geq .70$), sufficient test-retest reliability for the parameters that were analyzed in this study ($r \geq .55$ for C-CPT; $r \geq .74$ for TOVA), and good sensitivity to stimulant efficacy [105, 106].

Five parameters resulting from the C-CPT as well as the TOVA were analyzed at baseline, after 72 mg of placebo medication and after 72 mg of OROS-mph: hit reaction time (HRT), reaction time variability (RTV), commission errors (CEs), omission errors (OEs), and d-prime (DP). The HRT represents the average duration in milliseconds between target and correct response. Both low and high HRT are clinically relevant: very fast responses indicate impulsivity and very slow responses indicate inattention. The RTV measures the variability of the mean correct response times. Lower RTV indicates more consistent reaction times. CEs are made when the subject fails to inhibit a response to a non-target. High CE rates indicate impulsivity. OEs occur when the subject did not respond to a target. A high OE rate indicates inattention and/or low vigilance. The parameter DP reflects the subject’s discriminative ability between targets and non-targets (i.e., the CEs:OEs ratio) with lower scores indicating worse results.

For EF severity, we compared our data to norm data as listed in the C-CPT and TOVA manuals, resulting in standardized test scores (i.e., a $t$-score) per parameter. The C-CPT normative non-clinical sample comprised 1,920 individuals from the general population of whom 47% was male and ages ranged from 6 to 55+ years old [105]. The TOVA norm sample was recruited from colleges and adult community settings, and contained 250 individuals of whom 31% was male and ages ranged from 20 to 80+ years old [106]. Both normative samples were free of individuals with any central nervous system disorders or injuries.

**Subjective response**

Clinical response was measured every week using the validated ADHD rating scale (ADHD-RS) [107], a 18-item self-reported questionnaire about the severity of the DSM-IV ADHD symptoms inattention, hyperactivity, and impulsivity during the past week. Following Kooij et al. [98], reformulation of five complex statements into two single statements resulted in a reliable 23-item ADHD-RS self-report. Items were rated on a 4-point Likert scale (Total Score range 0-54). Reduction in the ADHD Total Score of at least 30% at follow-up was indicative for a clinically relevant response to OROS-mph [61].
Statistical analysis

CPT performance after medication

The prevalence of EF deficits was studied by calculating the proportions of the sample exceeding the clinical normative cutoffs on the five C-CPT and TOVA parameters (HRT, RTV, CE, OE, and DP) at baseline (i.e., \( t > 54 \) for C-CPT parameters, and \( t < 90 \) for TOVA parameters [105, 106]). Medication efficacy was tested by calculating the differences in raw test scores between conditions (i.e., baseline vs. placebo, baseline vs. OROS-mph, and placebo vs. OROS-mph), which we defined as the delta scores. Paired samples \( t \)-tests were used to compare the mean delta scores. Despite of randomization, we checked for medication order and CPT test order effects, by performing paired-samples \( t \)-tests.

Identification and predictive value of CPT parameters

We tested which CPT parameter(s) indicated OROS-mph efficacy best. First, clinically relevant OROS-mph effects on specific CPT parameters were identified by calculating Cohen’s \( d \) effect sizes (mean CPT delta score divided by the estimated standard deviation of the delta score). However, for clinical purposes we were particularly interested in the predictive value of OROS-mph effects on neuropsychological test performance. We therefore investigated whether EF severity impacted the medication efficacy on CPT delta scores, using linear regression models. EF severity was defined as the patient’s standardized CPT test score \((t\text{-score})\) at baseline. For parameters showing significant \([\text{medication} \times \text{EF severity}]\) interactions, a median split on EF severity stratified the sample into patients with clinical EF deficits (i.e., \( t \)-score below the median; EF\(_{\text{clinical}}\)) and patients without clinical EF deficits (i.e., \( t \)-score above the median; EF\(_{\text{non-clinical}}\)). Then, linear regression models were repeated using the dichotomized EF severity, in order to determine a moderation effect. Finally, we investigated whether heterogeneity of EF impacted OROS-mph effects. EF heterogeneity was defined as the number of clinically deficient EF areas at baseline. Three categories of EF heterogeneity were identified in our sample: patients without any EF deficits (EF\(_{\text{none}}\)), patients having EF deficits on one or two parameters (EF\(_{\text{one or two}}\)), and patients having EF deficits on three or more parameters (EF\(_{\text{multiple}}\)). Per CPT parameter, differences between these three groups were analyzed by means of nonparametric Kruskal-Wallis Tests and Mann-Whitney post-hoc tests, using CPT delta scores (placebo vs. OROS-mph) as dependent variables. Bonferroni corrections adjusted significance for multiple testing.
**Objective vs. subjective measures**

We analyzed the subjective efficacy of OROS-mph, and any relationship between objective and subjective measures of medication effects. First, rates of change on the ADHD-RS Total Score (i.e., the ADHD-RS delta scores) between baseline, placebo and OROS-mph were studied. Second, we correlated the placebo vs. OROS-mph CPT delta scores with the ADHD-RS delta score, using Pearson’s correlation coefficient \( r \). Then, the impact of ADHD severity (i.e., baseline ADHD-RS Total Score) as a moderator of medication effects on CPT test scores was investigated, using linear regression models. Again, for CPT parameters showing significant interaction effects, a median split divided the sample into patients with mild ADHD symptoms (i.e., scoring below the median; ADHD\textsubscript{mild}) and patients with severe ADHD symptoms (i.e., scoring above the median; ADHD\textsubscript{severe}), whereupon separate linear regression models were performed per ADHD group.

SPSS 18.0 (Chicago, IL) was used for data analysis. An \( \alpha \)-level of \( \leq 0.05 \) (two-sided) indicated statistical significance. Interaction effects were significant at an \( \alpha \)-level of \( \leq 0.10 \) (two-sided).

**RESULTS**

**Baseline general characteristics**

A total of 27 individuals participated in the study\(^1\), of whom \( n=5 \) dropped out (see Figure 1). We found no selection bias between participants and dropouts regarding sex, age, or baseline ADHD severity (\( p > 0.100 \)). Table 1 presents the baseline general characteristics of subjects who completed the study. Side effects were reported by ten subjects (46%) while using placebo. Irritability (\( n=5; 23\% \)) and insomnia (\( n=4; 18\% \)) were the most reported side effects. OROS-mph side effects were prevalent in 77% of the subjects (\( n=17 \)), who mostly reported decreased appetite (\( n=9; 41\% \)), a dry mouth (\( n=7; 32\% \)), weight loss (\( n=5; 23\% \)), headaches (\( n=5; 23\% \)), and nervousness (\( n=5; 23\% \)). Although substantially more side effects were reported in the OROS-mph group, the side effect rates were not significantly different between OROS-mph and placebo (Yates \( \chi^2=3.45, \ p=0.063 \)), but the types of side effects did. Three subjects discontinued treatment

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1 Sample size calculations were based on the study findings of Boonstra et al. [108], where a large baseline vs. IR-mph effect was found on the number of CEs on the Conner’s CPT (effect size \( \eta^2 \approx 0.21; \) Cohen’s \( d=1.04 \)). In order to get a similar effect size of \( d=1.04 \), with a power of 0.80 and an \( \alpha \)-level of 0.01, applying a cross-over design with every subject receiving both the OROS-mph and the placebo condition, 22 subjects were needed.
due to OROS-mph side effects, while side effects on placebo were no reason to stop study participation.

**TABLE 1.** Baseline general characteristics of the total group of adults with ADHD, N=22

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total group N=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: female, n (%)</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>Age, M (SD)</td>
<td>30.5 (7.4)</td>
</tr>
<tr>
<td>Vocational status:</td>
<td></td>
</tr>
<tr>
<td>Lower vocational training, n (%)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Higher secondary school, n (%)</td>
<td>11 (50.0)</td>
</tr>
<tr>
<td>Pre-university education, n (%)</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Higher professional school, n (%)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>University, n (%)</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>ADHD severity (ADHD-RS Total Score) *, M (SD)</td>
<td>30.2 (6.3)</td>
</tr>
<tr>
<td>Psychiatric history, n (%), of which:</td>
<td></td>
</tr>
<tr>
<td>Mood disorder, n (%)</td>
<td>17 (77.3)</td>
</tr>
<tr>
<td>Anxiety disorder, n (%)</td>
<td>11 (50.0)</td>
</tr>
<tr>
<td>Substance abuse disorder, n (%)</td>
<td>9 (40.7)</td>
</tr>
<tr>
<td>Eating disorder, n (%)</td>
<td>1 (4.5)</td>
</tr>
</tbody>
</table>

Note. N=total sample size; n=group size; %=percentage of total group; M=mean; SD=standard deviation; ADHD-RS=ADHD-Rating Scale.

* ADHD-RS Total Score ranges from 0 to 54 points.

**EF deficits in adults with ADHD**

At baseline, 20-60% of the subjects reported EF deficits on any of the five CPT parameters of either CPT. Specific rates of $E_{\text{clinical}}$ for the C-CPT parameters were: HRT (n=9; 41%), RTV (n=5; 23%), CEs (n=12; 55%), OEs (n=2; 9%) and DP (n=9; 41%). On the TOVA parameters these were: HRT (n=6; 27%), RTV (n=13; 59%), CEs (n=6; 27%), OEs (n=9; 41%), and DP (n=9; 41%).

**Objective efficacy of OROS-mph**

Table 2 presents the objective efficacy of placebo medication and OROS-mph on the five parameters of the C-CPT and TOVA. Compared to the baseline condition, OROS-mph significantly improved neurocognitive performance on the parameters RTV, CE and DP of both CPTs (all $p<.05$). When corrected for placebo effects, OROS-mph only showed a significant difference on C-CPT RTV ($t=-2.354, p=.029$). Comparisons between scores on different ISIs of the C-CPT, and between scores on halves or quartiles of the TOVA were non-significant.
Despite of randomization, we found an unexpected medication order effect, where subjects receiving OROS-mph first showed significantly more improvement on C-CPT and TOVA OE (p=0.005 and p=0.043 respectively), CE (p=0.017 and p=0.038 respectively), and C-CPT DP (p=0.031). A CPT order effect was also found, indicating a learning effect: the second CPT test showed better test scores, irrespective of the type of CPT test performed (C-CPT RTV: p=0.020; C-CPT CE: p=0.003; and TOVA DP: p=0.047). However, CPT order effects were only observed in the OROS-mph group, not in the placebo group.

Parameter sensitivity

For both CPTs, the largest baseline vs. OROS-mph effect sizes were found on the parameters RTV, CE, and DP (all between d=0.49–0.74; see Table 2). When corrected for placebo, effect sizes of OROS-mph were the strongest for the parameter DP (C-CPT and TOVA both d=0.40). For the C-CPT delta scores, a significant linear relation between medication condition and EF severity was found for the parameters RTV (F=6.297, p=0.001, R²=0.326), DP (F=2.937, p=0.045, R²=0.184), OE (F=9.085, p<0.001, R²=0.875), and CE (F=3.567, p=0.028, R²=0.206), but not for HRT (F=0.526, p=0.667, R²=0.039). A main effect was found for medication condition on the parameter C-CPT OE (β=-4.421, t=3.928, p<0.001). Moreover, EF severity moderated OROS-mph effects on the parameters C-CPT RTV (β=-0.184, t=-2.277, p=0.028), and C-CPT OE (β=-0.098, t=-4.759, p<0.001), indicating that subjects with clinical EF deficits profited more from OROS-mph, than did subjects with non-clinical EF deficits.

For the TOVA delta scores, the linear regression models were significant for the parameters RTV (F=7.827, p<0.001, R²=0.370), HRT (F=3.278, p=0.031, R²=0.197), OE (F=6.298, p=0.001, R²=0.321), and CE (F=3.742, p=0.018, R²=0.219), but not for DP (F=2.376, p=0.084, R²=0.151). Main effects for medication condition were found on TOVA RTV (β=-68.366, t=-2.562, p=0.014) and HRT (β=-154.066, t=-2.028, p=0.049). Furthermore, medication condition significantly interacted with EF severity on the parameter TOVA RTV (β=0.670, t=2.097, p=0.042), which after stratification resulted in significantly more favorable results for OROS-mph in the EFclinical group (F=4.638; β=-27.727; t=-2.154; p=0.044).

In summary, the many near-significant trends we found in expected directions implicate a plausible association between OROS-mph effects and the severity of EF deficits, mainly for the attention-related parameters RTV and OE (R²=0.320 or higher on both CPTs). None of the hyperactivity/impulsivity parameters significantly linked OROS-mph effect to EF severity, and proportions of declared variance were small (R²=0.220 or lower on both CPTs).
Heterogeneity of EF
Subdivision of our subjects into groups of EF heterogeneity on the C-CPT led to classification of n=4 subjects in the EFD\_none, n=14 subjects in the EFD\_low, and n=4 subjects in the EFD\_multiple group. For the TOVA, these were EFD\_none=6, EFD\_low=8, and EFD\_multiple=8, respectively. The groups of EF heterogeneity only differed on the parameter C-CPT OE ($H(2)$=8.940, $p=.011$), where significantly more improvement on OROS-mph was found for the EFD\_multiple group as compared to the EFD\_none group ($U=6.500, p=.009; r=-.65$) and the EFD\_low group ($U=36.500, p=.009; r=-.43$). Figure 2 presents the mean delta scores for the groups of EF heterogeneity separately, on the sensitive parameters HRT, RTV, and OE.

Objective vs. subjective efficacy of OROS-mph
Figure 3 shows the subjective efficacy of OROS-mph. Most subjects reported increased ADHD symptoms after using placebo medication, which significantly differed from the OROS-mph condition where all subjects reported decreased ADHD symptoms (68.2% vs. 0.0%; $\chi^2=19.83, p<.001$). Also, significant differences were found in the proportions of subjects reporting a clinically significant decrease of ADHD symptoms (i.e., decrease of 30% or more), which was five times higher in the OROS-mph condition (45.5% vs. 9.1%; $\chi^2=5.61, p=.018$). There was a poor relationship between objective and subjective efficacy of OROS-mph, except for the parameter TOVA RTV ($r=.447, p=.037$). Linear relations of medication condition and ADHD severity were found on TOVA RTV ($F=4.655, p=.007, R^2=.259$) and TOVA HRT ($F=3.800, p=.017, R^2=.222$) delta scores. ADHD severity significantly interacted with medication condition on the parameters TOVA RTV ($\beta=-3.226, t=-2.340, p=.024$) and TOVA HRT ($\beta=-5.413, t=-1.875, p=.068$). Stratified regression analyses showed more favorable results for OROS-mph in the ADHD\_severe group, on delta scores of TOVA RTV (mean delta score -15.542 vs. -7.650; $F=6.363, \beta=-30.750, t=-2.523, p=.019$) as well as TOVA HRT (mean delta score -9.958 vs. 6.650; $F=3.914, \beta=-53.750, t=-1.978, p=.061$). Patients with more severe ADHD symptoms profited more from OROS-mph than did patients with mild ADHD symptoms.
<table>
<thead>
<tr>
<th>C-CPT</th>
<th>Δ Baseline (ref) vs. placebo</th>
<th>Δ Baseline (ref) vs. OROS-mph</th>
<th>Δ Placebo (ref) vs. OROS-mph</th>
<th>Paired samples t-test Baseline vs. placebo</th>
<th>Paired samples t-test Baseline vs. OROS-mph</th>
<th>Paired samples t-test Placebo vs. OROS-mph</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>t  p  d</td>
<td>t  p  d</td>
<td>t  p  d</td>
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<tr>
<td>HRT</td>
<td>-3.80 (47.89)</td>
<td>-1.05 (37.64)</td>
<td>4.92 (49.85)</td>
<td>-0.373 .713 0.08</td>
<td>-0.127 .900 .03</td>
<td>0.452 .656 0.36</td>
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<td>RTV</td>
<td>-0.52 (2.80)</td>
<td>-2.40 (3.62)</td>
<td>-1.84 (3.58)</td>
<td>-0.871 .394 0.19</td>
<td>-3.040 .006 .66</td>
<td>-2.354 .029 0.38</td>
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<td>CE</td>
<td>-2.64 (7.34)</td>
<td>-4.62 (6.28)</td>
<td>-2.52 (7.75)</td>
<td>-1.608 .107 0.36</td>
<td>-3.370 .003 .74</td>
<td>-1.492 .151 0.3</td>
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<td>OE</td>
<td>-1.23 (2.56)</td>
<td>-1.76 (4.55)</td>
<td>-0.48 (2.27)</td>
<td>-2.247 .036 0.48</td>
<td>-1.775 .091 .39</td>
<td>-0.960 .348 0.33</td>
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<td>DP</td>
<td>0.18 (0.44)</td>
<td>0.33 (0.51)</td>
<td>0.16 (0.60)</td>
<td>1.964 .083 0.41</td>
<td>2.970 .008 .65</td>
<td>1.240 .229 0.40</td>
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<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>t  P  d</td>
<td>t  P  d</td>
<td>t  P  d</td>
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<tr>
<td>HRT</td>
<td>13.05 (59.35)</td>
<td>-1788 (6785)</td>
<td>-30.91 (85.15)</td>
<td>1.031 .314 0.22</td>
<td>-1.235 .231 .26</td>
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<td>-4.50 (19.13)</td>
<td>-19.41 (39.79)</td>
<td>-14.91 (38.38)</td>
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<td>-2.288 .033 .49</td>
<td>-1.801 .086 0.38</td>
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<td>CE</td>
<td>-2.50 (11.60)</td>
<td>-5.45 (9.85)</td>
<td>-2.95 (9.45)</td>
<td>-0.395 .324 0.22</td>
<td>-2.597 .017 .55</td>
<td>-1.467 .157 0.3</td>
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<td>OE</td>
<td>-0.50 (5.93)</td>
<td>-2.77 (9.70)</td>
<td>-2.27 (8.83)</td>
<td>-1.011 .679 0.08</td>
<td>-1.341 .194 .29</td>
<td>-1.562 .133 0.33</td>
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<td>DP</td>
<td>0.07 (1.34)</td>
<td>0.63 (1.29)</td>
<td>0.56 (1.39)</td>
<td>0.253 .803 0.05</td>
<td>2.278 .033 .49</td>
<td>1.878 .074 0.40</td>
</tr>
</tbody>
</table>

Note: OROS-mph-OROS-methylphenidate; Δ=delta or change scores between two measurements; ref-reference scores; M=mean; SD=standard deviation; HRT=hit reaction time; RTV=reaction time variability; CE=commission errors; OE=omission errors; DP=d-prime; t=t-value resulting from paired samples t-test; p=p-value for paired samples t-test; d=d-effect size as measured by Cohen’s d.

* For all CPT parameters, except for d-prime, lower scores indicate a better performance.
FIGURE 2. Mean delta scores on C-CPT and TOVA HRT, RTV and OE for patients having no, few or multiple EF deficits at baseline. Note. Baseline is used as the reference category, the lines illustrate the mean delta scores for baseline vs. placebo, and baseline vs. OROS-mph. * Significant difference between groups of heterogeneity at an α-level of .017, following a Bonferroni correction for multiple comparisons.
FIGURE 3. Increases or decreases of self-reported ADHD symptoms as measured with the ADHD-Rating Scale Total score after placebo or 72 mg OROS-mph medication, as compared to baseline.

Note. Baseline is used as the reference category. OROS-mph=osmotic-release methylphenidate. * Significant differences between baseline and OROS-mph at an α-level of .05 or smaller.

DISCUSSION

In this randomized double-blind cross-over placebo-controlled trial, we investigated the sensitivity of specific CPT parameters for measuring OROS-mph efficacy, in order to give insight into the neuropsychological endophenotype underlying the construct of ADHD. To our knowledge, this is the first study to objectively investigate the effects of a long-acting methylphenidate on neurocognitive test performance of adults with ADHD.

In our study, 20-60% of adults with ADHD had EF deficits, which is in line with a prevalence rate of 40% reported earlier in the study of Biederman et al. [17]. The large variance in the occurrence of EF deficits highlights the heterogeneity of EF deficits in this patient group [109], as the EF deficiency highly depends on which EF areas are being tested [16, 19]. Subdividing our sample into small groups of EF heterogeneity indicated that diversity in EF deficiency may also play a role in OROS-mph efficacy, but this needs to be investigated in larger samples.

In general, OROS-mph had apparent, positive effects on performance. OROS-mph clinically diminished the number of ADHD symptoms [110, 111], and even more interesting, OROS-mph clearly improved the objective neuropsychological test performance as compared to baseline conditions. Despite a low power,
OROS-mph significantly outperformed placebo on RTV in one of two CPTs, and was near-significantly superior on the other CPT as well. OROS-mph efficacy resulted in medium to high effect sizes, comparable to those found for immediate-release methylphenidate (IR-mph) [108]. The variability in reaction times (RTV), commission errors (CEs) due to impulsive reactions, and detectability ratio between targets and non-targets (d-prime; DP) were most sensitive for OROS-mph efficacy.

Digging one layer deeper, on the neural systems level endophenotypic for ADHD, the parameters RTV, HRT, and OE predicted OROS-mph efficacy. These parameters all aim at measuring the construct of attention [105, 106], and have shown to overlap in prior studies [83, 112]. Of these, RTV was the only parameter relating severity of ADHD behavior to neuropsychology, by showing more beneficial OROS-mph effects for subjects with worse EF deficits and more ADHD symptoms [87]. In a previous study, subjective ratings and objectively measured EF deficits were only weakly related [17], and likely to assess different levels of EF [21]. The fact that our study did find an association, emphasizes that RTV reflects a broad, underlying indicator for overall EF deficiency, on a neuropsychological level as well as a behavioral level.

Consistent with our findings, RTV has been identified as one of the most consistently deficient CPT parameters in children and adults with ADHD, highly responsive to stimulation medication [20, 113]. RTV specifically measures sustained attention, which fluctuates heavily in patients with ADHD [112]. Elevated RTV is characteristic of ADHD, but was observed in other psychiatric populations as well [20]. In neuropsychology, RTV is regarded a general deficiency in information processing and functional integration, especially in the area of attention, which coincides with several other cognitive deficits [114, 115].

Several fMRI studies examining brain activation during CPTs emphasize the relevance of the RTV parameter as well. Overall, this research found unnecessary activation of higher-order cognitive networks (i.e., putting too much cognitive effort into the task) in individuals with high RTV, while activating networks with a low cognitive effort – like the motor cortex – would be more efficient [20]. Furthermore, an insufficient suppression of the resting-state default mode network (DMN) during stimulus presentation was seen in ADHD children [116]. Moreover, ADHD patients’ DMN had a higher intensity and less functional connectivity, and less task-positive activation in frontal regions during tasks
when compared to healthy controls [117]. ADHD patients thus appear to possess 'dual deficits' during cognitive tasks: more resting-state activation on the one hand and less task-related activation on the other hand [20]. As a consequence of both deficits, the task-negative network and the task-positive network constantly compete [116], inducing lapses of inattention, a high RTV and more OEs [20, 118]. Strikingly, RTV and omission errors were also moderately related in the current study (Pearson's \( r = .526, p = .012 \)). The facts that methylphenidate treatment normalized DMN deactivation in ADHD children [93] and ameliorated the cognitive-attention network in adults with ADHD [119], may explain why OROS-mph mainly improved and had the highest effect on the attention-related neurocognitive parameters (i.e., RTV and OE) in our study. OROS-mph even led to cross-CPT learning effects, possibly by enhancing attention, by reducing test-related state anxiety [120], or by inducing a Hawthorne effect because of increased environmental awareness [121].

**Limitations**

A few limitations need to be taken into account. First, the small study sample size may have affected the generalizability of our findings, especially with regards to EF heterogeneity. Nevertheless, our within-subjects study design constitutes a strong study method for examining OROS-mph effects on individual differences in EF, that in themselves remain stable over time [85]. Second, although study methods differed regarding the type of mph (IR-mph vs. OROS-mph) and dosing of mph (weight-dependent vs. standardized amount), our effect sizes were lower than those of Boonstra et al. [108], on which the sample size calculations were based. In spite of the study being underpowered, near-significant trends in expected directions were found. Third, studying EF deficits with just two different CPTs may be considered a limited operationalization of the concept EF as a whole [85], although both CPTs show similar OROS-mph effects. Last, significant order effects were found for CPT order as well as medication order. Although CPT tests measure performance in highly standardized conditions, finding better results for the second administered CPT was consistent with Pietrzak et al. [92]. However, this learning effect was only found in the OROS-mph group, and may represent 'methylphenidate-enhanced attention' effects. Regarding medication order, non-response when using placebo may be better recognized by those who had OROS-mph first. Larger placebo effects in patients receiving placebo first are perhaps due to high treatment expectations or increased focus on the CPT.
Our study illustrated marked OROS-mph effects on neuropsychological test performance, that was best predicted by studying one single, non-specific, ADHD-characteristic CPT parameter: the reaction time variability (RTV). CPTs represent a simple but objective study method for measuring short-term efficacy of OROS-mph in adults with ADHD \[122\], and may provide more insight into clinical improvement on core ADHD symptoms than do subjective methods. Future studies extending the current neuropsychological knowledge in children with ADHD to large samples of adults with ADHD are encouraged, especially those linking CPT performance to methylphenidate effects in ADHD. These findings would increase our understanding of ADHD symptomatology, and ameliorate the monitoring of methylphenidate titration by looking at discrete changes in defined endophenotypic CPT parameters.