Methylphenidate effects on processing speed in a clinical sample of adults with ADHD and substance use disorder: a pilot study

Michel Arvidsson, Marja-Liisa Dahl, Johan Franck, Elisabeth H. Wiig and Niels Peter Nielsen

ABSTRACT

Background: Substance use disorders (SUDs) are common comorbidities of Attention Deficit Hyperactivity Disorder (ADHD). The most commonly prescribed medication for ADHD is methylphenidate. The clinical response to methylphenidate may be monitored against DSM-5 symptomatology, rating scales or interviews.

Aims: To evaluate the use of perceptual and cognitive processing speed measures to monitor methylphenidate effects in adults with ADHD and SUD.

Methods: A Quick Test of Cognitive Speed (AQT) monitored perceptual and cognitive processing speed in 28 adults with ADHD and SUD on treatment with methylphenidate before and after the morning dose.

Results: Twenty-six patients responded on AQT after the morning dose of methylphenidate. One-way ANOVA indicated significant treatment effects for color, form, and color-form combination naming, but not for shift cost values. Before the morning dose of methylphenidate, 92% were identified by cut-off time criteria for longer-than-normal processing times. After the morning dose of methylphenidate, 65% obtained color and form measures in the normal range for age peers. Only 35% obtained color-form processing measures in the normal range. Inter-individual response variability before medication intake was considerably larger than previously reported in studies of adults with ADHD only.

Conclusion: Proportionally, fewer adults with ADHD and SUD exhibited normalization of processing speed than previously observed for adults with ADHD without SUD. A potential clinical implication of the present study is that the AQT test may be used as a tool for dose-adjustment of central stimulants in the treatment of adults with ADHD and SUD.

Background

Substance use disorders (SUDs) are common comorbidities of Attention Deficit Hyperactivity Disorder (ADHD) in adults and may influence diagnostic identification and pharmacological treatment negatively. A recent study [1] evaluated adults with ADHD and SUD, who were actively using illicit substances and after a 2- to 3-month period of abstinence. Based on structured diagnostic interviews, the majority (95.3%) satisfied the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria both during illicit substance use and at reevaluation. This suggested that active substance use might not negate a diagnostic evaluation [1]. Withholding a diagnosis and appropriate treatment of ADHD in adults with SUD would appear contraindicated based on reports of lower odds for substance-related events during treatment with stimulants or atomoxetine [2]. Methylphenidate is the most commonly prescribed medication for ADHD in most countries, except in the United States [3]. Literature suggests, however, that the ADHD-SUD combination results in complex cases that may require increased dosing and outcomes that depend on the severity of ADHD and other psychosocial factors [4]. Early clinical trials of methylphenidate in adults with ADHD and comorbid SUD evaluated doses of up to 90 mg methylphenidate. This level of dosing may be insufficient and could explain the poor treatment effects seen in the trials [5,6].

Since long-term drug use may downregulate brain dopamine systems in chronic drug-dependent individuals, the need for higher doses to reduce ADHD symptoms could be explained by an increased tolerance to stimulants [7,8]. In Sweden, the average dose for ADHD-SUD patients is 40% higher than for patients with ADHD without SUD [8]. In a recent study [9] in adults with ADHD and amphetamine dependence, recruited from three medium-security prisons in Stockholm, a flexible dose range and higher maximum doses (180 mg) were used, and improved ADHD symptoms, clinical conditions, and retention in treatment were reported.

The clinical response to methylphenidate treatment for ADHD may be monitored against DSM-5 symptomatology,
rating scales or interviews [10]. However, in the present study, A Quick Test of Cognitive Speed (AQT) [11,12] was used to evaluate processing speed before and after the prescribed methylphenidate morning dose in adults with ADHD and SUD. AQT contains three tests with 40 visual stimuli in the form of randomized colored squares (black, blue, red, and yellow), forms (circle, line, square, and triangle); and combinations of colors and forms. The single-dimension processing and naming tests (Color, Form) measure perceptual speed. The dual-dimension processing and naming test (Color-Form) measures perceptual speed plus demands on executive functions, including attention, working memory and set shifting. Shift cost \[\text{Overhead} = \text{Color-Form} - (\text{Color} + \text{Form})\] reflects processing efficiency. Neuroimaging (rCBF and fMRI) revealed bilateral activation in the posterior temporal-parietal cortical and subcortical regions associated with attention, working memory, and set shifting and concurrent reduction of orbitofrontal cortical activation [13–18]. AQT has been norm-referenced for ages 15–85, has high test–retest reliability (0.91–0.95), and shows minimal change with age (about 1 s per decade) and minimal or no evidence of learning with repeated administrations [11,12,19–21]. Color-Form naming has been validated against neuropsychological measures [22–25]. In adults with ADHD, tested without medication, perceptual speed (Color, Form) may not be compromised, but there is typically a reduction in cognitive speed (Color-Form) and a larger-than-typical overhead, indicating added shift costs and reduced processing efficiency [10,26,21]. This pattern has been observed to occur in 85% of previously medicated adults with ADHD [10] and in 91–93% of medication-naïve adults with ADHD [21,26,27]. After treatment with methylphenidate, cognitive speed and shift costs are typically restored to within normal limits [10,26,27].

The aim of this study was to evaluate the effects of methylphenidate in adults with ADHD and comorbid SUD on perceptual and cognitive processing speed. We hypothesized that, before the morning dose of methylphenidate, cognitive speed, measured with dual-dimension color-form, would be significantly reduced and shift costs would be larger than typical. After the morning dose of methylphenidate, we hypothesized that cognitive speed would increase significantly, and shift costs would be significantly reduced.

**Methods**

**Participants**

The subjects were enrolled in a study (EMPHAS) with the primary aim to evaluate the pharmacokinetics of methylphenidate in blood and exhaled breath in adults with ADHD and SUD, and the AQT tests were administered as a part of the study. Patients were recruited from four psychiatric outpatient clinics within Stockholm Center for Dependency (Beroendecentrum Stockholm) during a period from May 2015 to May 2017. Twenty-eight adults (24 men and 4 women) with a mean age of 44.5 years (range, 28–56 years) participated in the study. Criteria for inclusion were that participants would (a) be between 18 and 64 years of age, (b) have received the same dose of methylphenidate medication for at least 2 weeks before the study, (c) were diagnosed with ADHD and comorbid substance abuse/substance dependence according to the DSM-IV criteria, (d) have signed informed consent forms, and (e) be capable of completing the required test protocols. The diagnoses of ADHD were made according to Swedish clinical standards and included assessments with structured psychiatric interviews and rating scales, such as Mini-International Neuropsychiatric Interview, M.I.N.I. [28] and Brown’s ADD Scale [29]. The psychological evaluation included the WAIS-IV measures of verbal and non-verbal intelligence, working memory, performance memory, performance and performance speed [30]. The D-KEFS Color-Word Interference and Trail Making Test [31] and T.O.V.A. [32] were also administered in most cases. Twenty-seven subjects enrolled in the study had been abstinent from narcotics for more than 3 months and one subject had been abstinent from narcotics for more than 1 month. The most common drugs of abuse before treatment with methylphenidate for ADHD were amphetamine (16 subjects) and heroin (9 subjects).

The study was conducted according to the Declaration of Helsinki (Fortaleza, 2013) and, as applicable, to the International Conference on Harmonization guidelines for Good Clinical Practice (UCH-GCP). Ethical approval was obtained from the Stockholm Regional Ethics Review Board (No 2013-002720-16).

**Materials and procedures**

The experimental measures were obtained with the AQT Color, Form, and Color-Form processing speed tests. The AQT tests were performed on two occasions, once before the morning dose of methylphenidate, between 8 and 11 AM, and again after 2–3 h, to evaluate the effects of methylphenidate on processing speed. The participants received methylphenidate (Ritalin, Concerta, Medikinet, or combinations of these) in varying morning doses, as prescribed by their respective physician, ranging from 20 to 216 mg with a mean dose of 101.43 mg (SD = 57.71 mg) (Table 1). The total daily dose could be higher as some patients also were prescribed additional methylphenidate doses later during the day. A urine toxicology test (screening and verification of amphetamine, benzodiazepine, buprenorphine, cannabis, cocaine, methadone, and morphine/heroin) was performed in the morning of the study day. Seven subjects were on methadone maintenance treatment for opioid dependence and all seven subjects tested positive for methadone. Five subjects were prescribed buprenorphine for opioid

| Table 1. Methylphenidate morning doses (mg) of the 28 study subjects (mean ±101.43 mg; SD = 57.71 mg). |
|-------------|-------------|-------------|-------------|-------------|-------------|
| T. Ritalin (IR) | 40;120 | T. Concerta (MR) | 54;27;72;108;162;200;216 | T. Medikinet (IR) | 30;60;120 |
| C. Ritalin (MR) | 20;40;60;60;80;80;80;100;160 | C. Medikinet (MR) | 60 | C. Medikinet (MR) | 40;72;40/72 |
| T. Ritalin/T. Concerta | 40/72;40/72 | | | | |
dependence, and six subjects were positive for buprenorphine in urine. Five subjects were prescribed benzodiazepines (oxazepam, diazepam) and nine subjects were positive for benzodiazepines in urine.

**Data Analyses**

Naming times (s) on the three AQT tests and for the overhead served as the dependent variables and the treatment conditions, before and after the morning dose of methylphenidate, as the independent variables. Normality tests (Shapiro–Wilk W) accepted normality for the color, form, and color-form naming-time distributions before medication but rejected normality after medication. As a result, all naming time measures underwent lognormal (ln) transformation and normality was accepted for all distributions. One-way ANOVA was used to evaluate the significance of mean differences between the treatment conditions (before and after the morning dose of methylphenidate) for each dependent variable, using the StatPlus: Mac Pro v5.9.92 (Analyst Soft Inc., Walnut, CA) software. Correlation coefficients (Pearson $r$) evaluated associations between the perceptual speed measures (color, form) and the cognitive speed measure (color-form). Null hypotheses were rejected at the a priori set $<0.01$ levels of significance to minimize positive bias.

**Results**

**Total Group**

Thirty-nine percent of the subjects were treated with morning doses of methylphenidate higher than the maximum daily doses (80 mg) included in the Summary of Product Characteristics by the Swedish Medical Products Agency (Table 1). Before the morning dose of methylphenidate, the means (s) in the total group ($N = 28$) for color (mean $= 31.71$; SD $= 7.72$) and form (mean $= 39.25$; SD $= 9.85$) were about 5 s and 9 s, respectively, longer than the upper limit of the normal range (i.e. $>25$ s and 30 s, respectively). For color-form naming the mean was 78.14 s (SD $= 19.47$), 8 s longer than the lower limit of the atypical range (i.e. $>70$ s + 2 SD), as compared to healthy adults [12,19,20]. After the morning dose of methylphenidate, the means for color (mean $= 25.36$; SD $= 5.71$) and form (mean $= 30.93$; SD $= 7.67$) were at the upper limit of the normal range, whereas the mean for color-form (mean $= 66.39$; SD $= 20.18$) was 6 s above the limit of the slower-than-normal range (i.e. $>60$ s). The overhead (shift cost) mean before the morning dose (11.79; SD $= 9.00$) was at the lower limit of the atypical range (i.e. $>10$ / $>2$ SD) and remained so after the morning dose (mean $= 12.89$; SD $= 13.09$), as compared to healthy adults [21]. Correlations (Pearson $r$) indicated that color and form naming times (ln) contributed about equally ($r = 0.72$ and $r = 0.69$, respectively) to color-form naming time.

One-way ANOVA first compared each measure (ln) before and after the morning dose of methylphenidate for the total group. For the total group, one-way ANOVA indicated significantly longer naming times before than after the morning dose of methylphenidate for color ($F_{1,55} = 13.32; p = .006; \eta^2 (2) = 0.20$), form ($F_{1,55} = 12.98; p = .007; \eta^2 (2) = 0.19$), but not for color-form ($F_{1,55} = 5.98; p = .02; \eta^2 (2) = 0.10$). The overhead value (shift cost) before the morning dose of methylphenidate was large (mean $= 14.92$ s; SD $= 12.53$ s) and remained so after the morning dose (mean $= 11.79$ s; SD $= 11.25$ s) and there was no difference between the conditions.

Review of the individual processing-speed measures before and after the morning dose of methylphenidate identified two non-responders for whom the form and color-form measures and overhead values (shift cost) were within the $\pm 3$ s ranges. One subject had color, form, and color-form naming times and shift cost in the normal range. The second subject was prescribed benzodiazepines and had atypical naming times for color, form, and color-form both before (i.e. 38 s, 44 s, and 114 s, respectively) and after the morning dose of methylphenidate (i.e. 34 s, 45 s, and 137 s, respectively). The two non-responders were removed from all subsequent data analyses, resulting in a final sample of 26 responders to medication.

**Responders**

Before the morning dose of methylphenidate, the means for color and form naming for the responders were in the slower-than-normal range (i.e. $>25$ s and 30 s, respectively) and the mean for color-form naming in the atypical range (i.e. $>70$ s + 2 SD) (Table 2), compared to norms for the age range [17,18]. After methylphenidate medication, the means for color and form approached the normal range (i.e. 25 and 30 s, respectively), but the mean for color-form naming remained in the slower-than-normal range (i.e. $>60$ s). The overhead shift-cost value $[CF - (C + F)]$ was in the larger than typical range (i.e. $>5$ s) before the morning dose of methylphenidate and remained so after methylphenidate medication. For the responders, the mean standard errors before and after the morning dose of methylphenidate were 1.55 and 1.11 s for color, 1.99 and 1.44 s for form, and 3.41 and 2.74 s for color-form. Correlations (Pearson $r$) indicated that color and form naming times (ln) contributed equally ($r = 0.74$ and $r = 0.72$, respectively) to color-form naming time.

For the responders, one-way ANOVA indicated significantly longer naming times (s) before than after the morning dose of methylphenidate for color ($F_{1,50} = 12.82; p = .001; \eta^2 (2) = 0.20$) and form ($F_{1,50} = 13.54; p = .001; \eta^2 (2) = 0.21$). For dual-dimension color-form, the naming times also proved

|                      | Color, mean (SD) | Form, mean (SD) | Color-Form, mean (SD) | Overhead, mean (SD) |
|----------------------|------------------|-----------------|-----------------------|--------------------|
| Before the morning dose of methylphenidate | 31.54 (7.92)     | 39.08 (10.19)   | 75.31 (17.38)         | 10.15 (6.97)       |
| After the morning dose of methylphenidate   | 25.00 (5.66)     | 30.23 (7.37)    | 62.62 (13.97)         | 10.50 (9.28)       |

Table 2. Descriptive statistics for AQT Color, Form, Color-Form and Overhead (s) for the group of responders ($n = 26$).
longer before than after the morning dose of methylphenidate ($F_{1,50} = 8.15; p = .01; \eta^2(2) = 0.14$). There was no statistically significant difference between the overhead values (shift cost) before and after the morning dose of methylphenidate ($F_{1,50} = 0.31; p = .58$). The mean gain in color-form naming before versus after the morning dose of methylphenidate was 13.00 s (SD = 11.27; 25th – 75th % = 4.50–18.00 s). This gain corresponds to slightly less than two standard deviations compared to the average (SD = 7.2 s) for a normative sample of healthy adults ages 15–54 years and can be considered significant [20]. Figure 1 shows a scatter plot with regression lines of the individual color-form naming times in the responders to medication, pre- and post-treatment, ranked based on post-treatment time measures. Correlation coefficients (Pearson $r$) between color and color-form ($r = 0.74$) and between form and color-form ($r = 0.72$) naming times indicated similar contributions to the cognitive speed measure before the morning dose of methylphenidate. The correlation (Pearson $r$) between the amount of gain in color-form naming time after methylphenidate medication and naming time before the morning dose of methylphenidate (ln) was $r = 0.45$ ($p < .05$, Cohen’s $d = 0.99$), indicating that only 20% of the variability in gains could be explained by the baseline measure (no medication). Correlations (Spearman’s Rho) between methylphenidate dose (mg) and (a) gain (before morning dose – after morning dose, Rho = 0.09; $p = .67$), (b) color-form naming after methylphenidate medication (Rho = –0.05; $p = .82$), and (c) overhead (shift cost) (Rho = 0.01; $p = .95$) were non-

significant and the methylphenidate dose accounted for less than 1% of the variance in outcomes.

When we applied the cutoff time criteria for the normal performance range (i.e. color < 25 s, form < 30 s, color-form < 60 s, and overhead ± 5 s) [11,12] to the naming times for responders before the morning dose of methylphenidate [16–18], 92% exhibited slower-than normal or atypical times on two or more of the measures. After the morning dose of methylphenidate, 65% of the responders obtained color and form naming times that were within the normal range for age peers, while only 35% received color-form naming times that were in the normal range for age peers.

**Discussion**

This was the first study in which the AQT processing speed measures were used to evaluate processing speed and efficiency in a clinical sample of adults with ADHD and comorbid SUD on treatment with methylphenidate, before and after the morning dose of methylphenidate. We expected cognitive speed and processing efficiency to be more severely affected before the morning dose of methylphenidate than previously observed in adults with ADHD without SUD [25–28]. This expectation was based on the complexity of the physical, psychological or social factors associated with SUD [3,4]. The results confirmed our hypotheses and provided estimates of how comorbid ADHD and SUD might affect perceptual and cognitive processing and processing efficiency before and after the morning dose of methylphenidate.
methylphenidate. Importantly, methylphenidate dose could not adequately explain the gains in cognitive speed (color-form naming) or the shift cost outcomes.

A major limitation of the present study is that a control group of adults with ADHD but without SUD was not included for comparison. In lieu of this data, we first compared the outcomes of the present study with preliminary findings from a Swedish study of a methylphenidate dose effect for adults with ADHD without SUD [10], and found similarities as well as differences. In the controlled dose-monitoring study (n = 33), the average perceptual and cognitive speed measures before methylphenidate treatment were within the upper limits of the normal range established for healthy adults [10–12]. In the present study, the average perceptual processing speed measures (color and form) were slightly above the normal range, whereas the cognitive processing speed measure (color-form) was in the atypical range (i.e. >70 s/± 2 SD). The effect size (beta-squared) for the processing speed measures after treatment in this study was larger than in the controlled-dose-monitoring study for color (0.20 vs. 0.10) and form (0.19 vs. 0.11), but smaller for color form (0.14 vs. 0.20) [10]. This corresponds to the observation that the perceptual speed measures (color, form) were associated with relatively larger average gains after methylphenidate treatment than the cognitive speed measure (color-form).

Comparison of shift costs (overhead) for responders before the morning dose of methylphenidate indicates a larger range in the present study (0–50 s) than in the controlled monitoring study (1–31 s) [10]. The average shift cost difference in the two studies was about 4 s (i.e. mean = 11.79 s and 7.55 s, respectively), and the variability was considerably larger in the current than in the controlled monitoring study (SD = 9.0 s and 6.68 s, respectively) [10]. In both studies, the shift costs before the morning dose of methylphenidate were in the atypically large range compared to normative data for healthy adults [21]. In the controlled monitoring study, used for comparison, shift costs were normalized (i.e. <3 s) with methylphenidate (40 mg Medikinet R) [10]. In the current study, shift costs did not change after the morning dose of methylphenidate, indicating that processing efficiency was not significantly affected.

The sensitivity of the AQT processing speed tests for detecting larger than normal color, form, color-form, and overhead measures without medication differed considerably in this and the controlled dose-monitoring study. In the present study, 92% of participants exhibited slower than typical cognitive speed (i.e. longer color-form naming times) and less than typical processing efficiency (i.e. larger shift costs) before methylphenidate treatment. In the controlled dose-monitoring study of previously medicated adults with ADHD without SUD, 82% exhibited slower than typical cognitive speed and less than typical processing efficiency before treatment with methylphenidate [10]. The sensitivity in the current study was, however, similar to that reported (i.e. 91% and 93%) in previous studies of medication-naive adults with ADHD before methylphenidate treatment [21,27].

A second controlled monitoring study of methylphenidate dose effects in twenty-eight adults with ADHD without SUD validated the results of the preliminary study [10,37]. This allowed us to combine the two study samples to include 43 men and 18 women, ranging in age from 17 to 60 years (mean = 34.2; SD = 12.5). The descriptive statistics for the 28 adults with ADHD and SUD and the combined sample of previously medicated adults with ADHD without SUD are shown in Table 3. Normative data for healthy adults, ages 18–70 years, indicate standard deviations of 3.39 s for color, 3.84 s for form, and 6.38 s for color-form combinations [26]. A comparison of means before methylphenidate treatment indicate that the differences are larger than +2 SD for color and form, and about +3 SD for color-form for the ADHD with SUD than for the ADHD without SUD group. After methylphenidate treatment, the mean difference was larger than +1 SD for color, +2 SD for form, and remained about +3 SD for color-form naming. In combination, these measures are of a size that supports the clinical significance of the observed differences.

From a clinical perspective, one of the findings of relevance in this study may be that perceptual speed (color-form) was normalized with methylphenidate in two-thirds of the responders. These measures reflect factors related to retrieval and verbal response time and, as a result, the better outcomes might be reflected in greater verbal fluency with methylphenidate. In contrast, cognitive processing (color-form) and processing efficiency (shift costs), associated with attention, working memory, and set-shifting capabilities, only improved to normal levels in one-third of the responders. This may reflect the effects of long-term substance abuse on the levels of cortical activation and degree of connectivity between specific regions of the brain and may have resulted in minimal cognitive processing speed improvements after treatment [33,34].

The study has several limitations. The methylphenidate dose was not fixed and the subjects were receiving their clinically prescribed morning dose and results should be interpreted in view of this limitation. In addition, possible relationships between the processing speed and commonly used neuropsychological ADHD assessments were not explored. Among other limitations, the period of time during which participants used substances or the amounts used...
were not accounted for and could therefore not be incorporated in multivariate analyses. Moreover, no distinction was made between ADHD of the predominantly inattentive or predominantly hyperactive or combined subtypes, as they might have shown different reactions to the stimulant medication [35]. The lack of a non-SUD ADHD comparison group with the same treatment protocol is a significant limitation to the validity of this study. However, as the intention was to gather preliminary support for further research in this patient category, from a clinical perspective, we are encouraged by the findings. A potential clinical implication of the present study is that the AQT test may be used as a tool for dose-adjustment of central stimulants in the treatment of adults with ADHD and SUD. Further research is required to validate the use of AQT in adults with ADHD and SUD, for example, by comparing processing speed using both AQT and a common neuropsychological test (e.g. Stroop Color-Word Test) [23,36] during the initiation period of central stimulant treatment (i.e. at baseline, once weekly until the target dose is reached) in adults with ADHD and SUD. We would also recommend to include a non-SUD ADHD group in future studies to increase the validity of such comparisons.

Acknowledgements

The authors thank Felix Strandberg and Inger Engman for excellent assistance during the study.

Disclosure statement

Dr. Niels Peter Nielsen reports grants for participation in professional meetings and conferences from Evelan Pharma AB, Danderyd, Sweden, during the conduct of the study. Nielsen and Wiig are coauthors of A Quick Test of Cognitive Speed (AQT). The copyright is held by AQT Assessments Aps. Copenhagen, Denmark. The other authors report no conflict of interest.

Funding

This study was supported by grants from the Stockholm County Council [ALF project 20150043] and the Swedish Research Council [2015-02836].

ORCID

Michel Arvidsson http://orcid.org/0000-0002-6645-3745

References

[1] van Emmerik-van Oortmerssen K, Vedel E, Kramer FJ, et al. Diagnosing ADHD during active substance use: feasible or flawed? Drug Alcohol Depend. 2017;180:371–375.
[2] Quinn PD, Chang Z, Hur K, et al. ADHD medication and substance-related problems. Am J Psychiatry. 2017;174:877–885.
[3] Raman SR, Man KKC, Bahmanyar S, et al. Trends in attention-deficit hyperactivity disorder medication use: a retrospective observational study using population-based databases. Lancet Psychiatry. 2018;5:824–835.
[4] Carpentier PJ, Levin FR. Pharmacological treatment of ADHD in addicted patients: What does the literature tell us. Harv Rev Psychiatry. 2017;25:50–64.
[5] Levin FR, Evans SM, Brooks DJ, et al. Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion and placebo. Drug Alcohol Depend. 2006;81:137–148.
[6] Levin FR, Evans SM, Brooks DJ, et al. Treatment of cocaine dependent treatment seekers with adult ADHD: double-blind comparison of methylphenidate and placebo. Drug Alcohol Depend. 2007;87:20–29.
[7] Volkow ND, Fowler JS, Wang GJ, et al. Dopamine in drug abuse and addiction. Arch Neurol. 2007;64:1575–1579.
[8] Skoglund C, Brandt L, D’Onofrio B, et al. Methylphenidate doses in Attention Deficit/Hyperactivity Disorder and comorbid substance use disorders. Eur Neuropsychopharmacol. 2017;27:1144–1152.
[9] Konstenius M, Jayaram-Lindstrom N, Gutierrez J, et al. Methylphenidate for ADHD and drug relapse in criminal offenders with substance dependence: a 24-week randomized placebo-controlled trial. Addiction. 2014;109:440–449.
[10] Nielsen NP, Wiig EH, Bäck S, et al. Processing-speed can monitor stimulant medication effects in adults with Attention Deficit Hyperactivity Disorder with Hyperactivity. Nordic J of Psychiatry. 2017;71:296–303.
[11] Wiig EH, Nielsen NP, Minthon L, et al. A Quick test of cognitive speed. San Antonio (TX): PsychCorp; 2002.
[12] Wiig EH, Nielsen NP, Minthon L, et al. A Quick test of cognitive speed. Et kort manual. Svensk version & Norsk versjon. Stockholm (Sweden): Harcourt/PsychCorp; 2005.
[13] Wiig EH, Nielsen NP, Minthon L, et al. Parietal lobe activation in rapid, automatized naming by adults. Percept Mot Skills. 2002;94:1230–1244.
[14] Warkentin S, Erikson C, Janciauskiene S. rCBF pathology in Alzheimer’s disease is associated with slow processing speed. Neuropsychologia. 2008;46:1193–1200.
[15] Turken A, Whitfield-Gabrieli S, Bammer R, et al. Cognitive processing speed and the structure of white matter pathways: convergent and long-term response to treatment with methylphenidate. Atten Defic Hyperact Disord. 2008;42:1032–1044.
[16] Esterman M, Chiu YC, Tamber-Rosneau BJ, et al. Decoding cognitive control in human parietal cortex. Proc Natl Acad Sci U S A. 2009;106:17974–17979.
[17] Berryhill ME, Chein J, Olson IR. At the intersection of attention and memory: the mechanistic role of the posterior parietal lobe in working memory. Neuropsychologia. 2011;49:1306–1315.
[18] Bueno V, da Silva MA, Alves TM, et al. Fractionating executive functions of adults with ADHD. J Atten Disord. 2017;21:944–955.
[19] Jacobson JM, Nielsen NP, Minthon L, et al. Multiple rapid naming measures of cognition: normal performance and effects of aging. Percept Mot Skills. 2004;98:739–753.
[20] Wiig EH, Nielsen NP, Jacobson J. A quick test of cognitive speed: patterns of age groups 15 to 95 years. Percept Mot Skills. 2007;104:1067–1075.
[21] Nielsen NP, Wiig EH. Validation of the AQT color-form additive model for screening and monitoring pharmacological treatment of ADHD. J Atten Disord. 2013;17:187–193.
[22] Nielsen NP, Ringström R, Wiig EH, et al. Associations between AQT processing speed and neuropsychological tests in neuropsychiatric patients. Am J Alzheimer’s Dis Other Demen. 2007;22:202–210.
[23] Fleck C, Wiig EH, Corwin M. Stroop interference and AQT cognitive speed may play complementary roles in differentiating dementias with frontal and posterior lesions. Community Ment Health J. 2015;51:315–320.
[24] Golden CJ, Freshwater SM. Stroop Color and Word Test: revised examiner’s manual. Wood Dale (IL): Stoelting; 2002.
[25] Nasreddine ZS, Phillips NA, Bédardien V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J American Geriatrics Soc. 2015;53:695–699.
[26] Nielsen NP, Wiig EH. AQT cognitive speed and processing efficiency differentiate adults with and without ADHD: a preliminary study. Int J Psychiatry Clin Pract. 2011;15:219–227.

[27] Wiig EH, Nielsen NP. A Quick Test of Cognitive Speed for comparing processing speed to differentiate adult psychiatric referrals with and without attention-deficit/hyperactivity disorders. Prim Care Companion CNS Disord. 2012;14.

[28] Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59:22–33.

[29] Brown T. Brown ADD Scales. Stockholm: NCS Pearson; 2004. Swedish.

[30] Wechsler D. WAIS IV: Wechsler Adult Intelligence Scale. 4th ed. Stockholm: NCS Pearson Inc. 2010. Swedish.

[31] Delis DC, Kaplan E, Kramer JH. D-KEFS: Delis-Kaplan Executive Function System. Stockholm: Harcourt Assessment; 2005. Swedish.

[32] Leark RA, Duouy TR, Greenberg LM, et al. Test of Variables of Attention (T.O.V.A.). Los Alamitos (CA): The TOVA Company; 2007.

[33] Shang CY, Sheng C, Yang LK, et al. Differential brain activations in adult attention-deficit/hyperactivity disorder subtypes: a counting Stroop functional MRI study. Brain Imaging Behav. 2018;12:882–890.

[34] Saad JF, Griffiths KR, Kohn MR, et al. Regional network organization distinguishes the combined and inattentive subtypes of Attention Deficit Hyperactivity Disorder. Neuroimage Clin. 2017;15:383–390.

[35] Reimherr FW, Marchant BK, Gift TE, et al. Types of adult attention-deficit hyperactivity disorder (ADHD): baseline characteristics, initial response, and long-term response to treatment with methylphenidate. Adhd Atten Def Hyp Disord. 2015;7:115–128.

[36] Stroop JR. Studies of interference in serial verbal reactions. Psychol Monogr. 1938;50:38–48.

[37] Magell G, Gustafsson J, Wiig EH, et al. Monitoring methylphenidate dose effects with AQT in adults with attention deficit disorder with hyperactivity: a validation study. J Neurosci and Neuropsychol. 2018;2:1–7.