Review of screening and monitoring treatment of ADHD in adults with processing-speed.

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Abstract

The review objective was to examine characteristics and clinical uses of processing-speed measures in the management of adults with attention deficit/hyperactivity disorder. Normative and clinical data indicate no gender bias, high test-retest reliability, and acceptable levels of concurrent validity required for neuropsychological assessment. Recurring patterns in color-form naming and overhead values for adults with ADHD differ from those of healthy adults and adults with depression without ADHD or with dementia. The processing-speed profiles indicate average-normal response times for single-dimension colors and forms, longer-than-average response times for color-form combinations, and larger-than-average overhead values. Independent studies that monitored methylphenidate dose effects in medication-naïve and previously-medicated adults with ADHD and ADHD substance use disorder indicate statistical differences between color-form naming times and overhead measures at baseline without medication and at endpoint with stimulant medication. Results suggest that the measures may complement observational ratings of ADHD symptomatology in screening and monitoring stimulant-medication effects.

Keywords: ADHD, Adults, Screening, Treatment, Stimulant medication, Dose optimization.

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Introduction

In daily primary care or psychiatric practice for adults, it can be difficult to administer complex neuropsychological tests for initial screening for Attention-Deficit Disorder with Hyperactivity (ADHD) or for monitoring the effects of pharmacological treatment. Clinical research suggests that the processing-speed and overhead (shift cost) measures obtained with A Quick Test of Cognitive Speed (AQT) [1,2] may prove useful as complementary clinical tools to screen and monitor the effects of treatment with methylphenidate in adults with suspected ADHD. Several factors seem to contribute to the potential clinical usefulness of the tests, some of which are inherent to the design and statistical characteristics of AQT. Other factors relate to the response profiles that appear able to differentiate between adults with Attention-Deficit Disorders with Hyperactivity (ADHD) and other neuropsychiatric disorders without ADHD. A third factor relates to observations that the AQT processing-speed and shift-cost measures appear to be able to quantify the effects of methylphenidate and define stabilization with medication in adults with ADHD.

In the general adult population, the prevalence of ADHD has been estimated to be between 2 and 3 per cent [3]. However, as many as 80% of adults with ADHD may present with one or more comorbid neuro-psychiatric disorders [4] among comorbidities that are commonly associated with ADHD are:

a) Depression, estimated to occur in between 20% and 50% of cases
b) Bipolar disorder estimated in from 5% to 47%
c) Anxiety or personality disorders estimated in about 50% of patients [3].

In addition, Substance Use Disorder (SUD) appears to occur twice as often in adults with ADHD as in the general population of adults [4]. The overlapping and sometimes potentially additive effects of ADHD and neuro-psychiatric comorbidities have led to proposals for using a dimensional, rather than a categorical, approach when diagnosing ADHD [4,5]. It may also be difficult to separate which functional domains may be affected by the attention, working memory and set-shifting deficits that are hallmarks of the symptomatology in ADHD, and which symptoms may be the result of an existing comorbidities or other factors. It is in this context that the AQT measures may be applicable to serve as complements to behavioral ratings and other qualitative observations.

We first noticed a recurring pattern in the AQT processing-speed and overhead (shift-cost) measures of adults with an ADHD diagnosis in daily psychiatric practice. The pattern that emerged was that the AQT color and form naming times, which primarily reflect reaction, retrieval and response time, tended to be within the average-normal range compared to norms for healthy adults [1,2]. In contrast, the naming times for color-form combinations, which add requirements for co-articulation and set shifting, tended to be in the slower-than-normal (>+1SD) or atypical (>+2SD) ranges compared to healthy adults in the same age range [1,2]. This caught our attention, because research of adults with dementia of the Alzheimer's type reported naming

times for color, form, and color-form that were in the slower-than-normal range in the mild-to-moderate disease stages and then showed a slowing of the rate of naming with the disease progression [6-8]. This indicated that both the perceptual (color, form) and cognitive speed (color-form) were affected negatively in adults with dementia and contrasted with our observations of average perceptual speed values for adults with ADHD.

The aims of this review are to:

a) Describe the design and statistical characteristics of AQT

b) Differentiate the processing- and naming-speed profiles observed in diagnostic groups with ADHD with and without depression, ADHD with comorbid Substance Use Disorder (SUD), and depression without ADHD

c) Explore patterns in outcomes after optimum treatment of adults with ADHD diagnoses with stimulant medication.

AQT Design and Statistical Characteristics

The AQT design is simple and easy to administer and interpret, and its closest parallel is the Color-Word Test (CWT) [9]. AQT features three test plates, each with 40 highly familiar visual stimuli, designed to elicit Rapid Automatic Naming (RAN) [1,2]. The first test plate (Test A) shows four familiar colors (*black, blue, red, yellow*), presented as circles in randomized order. The second (Test B) shows four familiar geometrical forms (*circle line, triangle, square*), presented randomly in black. The third test plate (Test C) features 40 combinations of the colors and forms (e.g., *yellow circle*) in randomized order. The total naming time (s) for each test is measured digitally, beginning at voice onset and ending after articulation of the last item. The two single-dimension naming tests (color, form) measure reactive attention and reflect a combination of reaction, retrieval and response time. The two-dimensional naming test (color-form) measures active attention, which also reflects increased demands on attention, working memory and cognitive control. Rapid naming of the color-form stimuli is associated with bilateral activation of the posterior regions of the temporal and parietal lobes and the occipital lobes, as indicated by rCBF [1,2] and by sagittal and coronal f-MRI images obtained at the Malmö University Hospital Brain Center. The cortical areas, activated during color-form naming, have been associated with central executive functions (attention-memory) and cognitive control (set shifting) [10-12]. This design allows for the calculation of overhead (shift cost) by using the formula [color-form time (s)-(color+form) time (s)], resulting in either a positive or negative value (+/-) and this measure is considered to account for the added co-articulation time and demands on executive functions and cognitive control [13].

The color, form and color-form combination naming time and overhead (shift cost) measures were norm and criterion-referenced for healthy speakers of American-English, Danish and Swedish, ranging in age between 18 and 85 years [1,2,13-15]. AQT shows a high degree of test-retest reliability in healthy adolescents and adults with correlations (r) of 0.91 for color, 0.92 for form, and 0.95 for color-form naming [1,2]. The tests show no gender bias or educational bias after literacy has been achieved with formal education (Grade 8) [1,2,14]. Over the age span between 15 and 60 years, color-form naming times are reported to increase about 1 s/decade and after age 60 by 1 s/seven years [14]. There is no evidence of learning or habituation in healthy adults during a period of 10 min repeated trials and the tests can therefore be re-administered with short time intervals [1,2]. The simple design allows for the test to be used across languages and cultures, and it has been norm-referenced with samples of adult speakers of other languages other than English and Danish/Norwegian/Swedish, among them, Italian, and Spanish [16,17]. The three processing-speed tests can be administered in person, using the printed test plates, or on a PC-format tablet being finalized, which records naming times and calculates overhead (shift cost) (AQT Assessment ApS, Denmark <clc@aqt.dk>).

Concurrent validity

The processing-speed tests and measures have been tested for concurrent validity with several commonly-used tests of cognitive functions. The outcomes indicate that the dual-dimension color-form naming test shows moderate levels of validity as a neuropsychological test and that the underlying construct differs from that of other commonly used tests. As examples, the dual-dimension naming measure correlates negatively with WAIS-IV Performance IQ (r=-0.61), Montreal Cognitive Assessment (MOCA) (r=-0.59) and MMSE (r=-0.72) scores ($p>0.01$) and the effect sizes are large [18,19]. The association between AQT color-form naming and Stroop interference T-scores is relatively low (r=-0.31; p=0.049). This finding points to considerable differences in the underlying constructs for the AQT cognitive speed and the Stroop inhibition measures [19].

Test-retest reliability

Whereas AQT shows a high degree of test-retest reliability in healthy adolescents and adults that may not apply to adults with ADHD. For this review, we evaluated the test-retest reliability of the color-form naming measure, which has been found to be sensitive to the ADHD symptomatology in adults [20-22]. Thirty-two previously-medicated adults with ADHD diagnoses, who participated in a methylphenidate dose-effect study, were used to establish test-retest reliability without medication and with methylphenidate [21]. The first test-retest administration occurred in the morning after two days without medication to obtain baseline measures. The tests were re-administered later in the day, approximately 1 hour after the ingestion of a maximum dose of methylphenidate IR, equivalent to 17.39/34.78 mg. At baseline, the test-retest means for color-form naming were 57.81s (SD=11.93) and 59.63s (SD=15.19) and with maximum methylphenidate the color-form means were 53.60s (SD=12.09) and 53.23s (SD=12.30), respectively. After lognormal (*ln*) transformation of naming times, the test-retest correlation at baseline without medication was r=0.89 ($p<0.001$). After stabilization with methylphenidate, the correlation increased to r=0.94 ($p<0.001$), a test-retest correlation that is similar to that of 95 reported for healthy adults [1,2]. The difference between the coefficients at baseline and endpoint (q=0.32) proved of

medium effect size and is therefore considered to be clinically relevant.

Gender bias

Among healthy adults, AQT has shown no gender bias but this might not be the case for adults with ADHD, as research has indicated gender differences in ADHD symptomatology in the direction that males show higher levels of impulsivity than females [23,24]. For this review, we explored potential gender differences in the AQT color, form and color-form naming times and overhead (shift cost) in 41 males and 19 females with ADHD diagnoses, who participated in studies that monitored the effects of two equal doses of methylphenidate IR [21,22]. The mean age for males was 33.90 (SD=13.07) and for females 31.47 years. (SD=12.92) and the groups did not differ in age (t56=1.20; p=0.24). The descriptive statistics for the processing-speed measures and overhead (shift cost) by males and females are shown in Table 1. The baseline and endpoint measures, after the ingestion of the maximum dose of methylphenidate IR (17.39/34.78mg) were used to compare the effects of gender before and after stimulant medication.

One-way ANOVA, after acceptance of normality, indicated statistical between-group effects for color (F3, 116=8.37; p=0.00004; η2=0.18), form (F3, 116=7.11;p=0.0002; η2=0.16), color-form (F3,116=15.44; p<0.0001; η2=0.29) and overhead (shift cost) (F3,116=6.56; p=0.0004; η2=0.15). However, post hoc analyses (Scheffe) indicated no statistical differences (p>0.05) in color, form or color-form naming times or in overhead between males and females either at baseline or at endpoint. As expected, males and females used longer color-form naming times and had larger overhead (shift cost) at baseline than at endpoint, indicating positive treatment effects. Taking into account that the sample was biased in favor of males, the preliminary findings suggest that possible gender differences in impulsivity among previously-medicated adults with ADHD did not influence the executive functions assessed by the perceptual-(color, form) or cognitive-speed (color-form) or overhead (shift cost) measures.

Response-Time Profiles

In two early clinical studies of stimulant-naïve adults with ADHD, ages 17-55 years, we used cut-off time criteria of <60s for the average range (<+1SD) for color-form naming and of <+/-6s for the average overhead (Shift cost) range (<+/-1SD) to explore if these measures differed from those observed in healthy adults [20,25]. At baseline without medication, 91% and 89% of the patients with ADHD in those studies were identified to exhibit longer-than-average form (>30s) or color-form naming times (>60s) and larger-than-average overhead (shift cost) (>+/-6s), when using the original norms as criteria [1,2].

With additional response-time profiles from younger adults with ADHD, in the age range from 17 to 55 years, it seemed relevant to re-analyse the accumulated normative data for healthy adults to validate the cut-off time criteria, we had used in earlier studies [20,25]. We analysed the color-form response-time and overhead (shift cost) of 180 healthy adults in two age cohorts, ages 18-34 years and 35-55 years, each with 90 adults [13,15]. One-way ANOVA, using *ln* values, indicated no statistical differences in color -form naming times or overhead (shift cost) values between the age cohorts. The upper limit of the average range for color-form, rounded to the nearest 5s, proved to be 55s (+1SD), slightly lower than earlier criterion of 60s, and the average range for overhead of +/-5s (+/-1SD) was slightly less than set earlier.

For this review we applied the lower cut-off time criterion (55s) for color-form and overhead (+/-5s) to the results from two studies that focused on the effects of controlled-dose methylphenidate treatment of patients with ADHD diagnoses, who were previously-medicated for 6 months or longer [21,22]. We combined the patient groups (n=40 and 21), since identical methods and procedures were used to monitor the effects of methylphenidate IR. Patients in the combined group (n=61) were off medication for two days before the tests were administered to obtain a baseline measure. In this group and with the revised criteria, 84% of patients were identified to have longer-than-average color-form (>55s) and/or larger-than-average overhead (>+/-5s) at baseline without medication.

To delineate possible differences in the response profiles of medication-naïve and previously-medicated adults with ADHD, who responded to stimulant medication, we compared naming-time and overhead (shift cost) measures at baseline and endpoint after optimum treatment with methylphenidate [20-22]. For the 64 medication-naïve adults with ADHD, who responded to medication, the baseline means were 24.63s (SD=4.45) for color, 29.50s (SD=6.09) for form, 66.69s (SD=11.12) for color-form, and 13.00s (SD=7.93) for overhead (shift cost). At endpoint the respective values were 19.95s (SD=3.21), 22.48s (SD=3.72), 45.84s (SD=7.46), and 3.4s (SD=3.84). In contrast, the baseline means for the previously-medicated adults (n=53) were 25.49s (SD 6.17) for color, 29.38s (SD 6.55) for form, 59.89s (SD=13.91) for color-form, and 4.77s (SD=8.84) for

Table 1. *Means and standard deviations for color, form and color-form naming and overhead (shift cost) (overhead (shift cost) (shift cost)) (s) without medication and with high-dose medication for 41 males and 19 females with ADHD.*

	Color		Form		Color-Form		Overhead	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Males								
No medication	25.63	-6.67	28.51	-9.28	59.17	-15.36	6.88	-5.4
High-dose	21	-3.67	23	-4.06	44.9	-7.07	3.59	-3.26
Females								
No medication	23.11	-5.17	27.53	-6.46	57.84	-10.68	8.57	-7.23
High dose	19.58	-3.7	21.84	-4.5	44.26	-8.84	3.68	-3.71

overhead (shift cost). At endpoint, the means were 20.81s (SD=3.74), 22.75s (SD=4.12), 45.28s (SD=7.60), and 1.81s (SD=3.09), respectively.

One-way ANOVA with *ln* values indicated no statistical differences between groups for color and form naming either at baseline or endpoint (p>0.05). In contrast, there were statistical between-group effects at baseline for color-form (F3, 230=50.63; p<0.0001; η^2=0.40) and overhead (shift cost) values (F3,230=38.83; p<0.0001; η^2=0.34) and the effect size was large. Post-hoc analysis at baseline, indicated that color-form naming times were longer (Scheffe=4.29; p=0.0005) and overhead values (shift) larger (Scheffe5.67; p<0.0001) for the stimulant-naïve than for the previously-medicated adults with ADHD. There was no statistical difference between the groups at endpoint, after a maximum dose of methylphenidate, for either color-form (Scheffe0.007; p=1.00) or overhead (shift cost) values (Scheffe=0.35; p=0.99). Rank-order correlations between the baseline and endpoint measures proved lower for the medication-naïve adults (Rho=0.62; t=6.24; p<0.01) than for the previously-medicated patients (Rho=0.83; t=10.43; p<001), indicating greater predictive efficiency in the latter group. Plots of individual color-form naming times, with linear regression lines, ranked on the basis of endpoint measures, are shown for the medication-naïve adults (n=64) and the previously-medicated adults (n=53) in Figure 1.

In a later study of 28 patients with ADHD and comorbid SUD, the AQT tests identified reductions of considerable magnitude in the color-form and overhead (shift cost) time measures [26]. At baseline without medication, the means for color (M=31.54s; SD=7.92) and form naming (39.08s; SD=10.19) were in the larger-than-average range (>25s and >30s, respectively) [2]. The mean for color-form (M=75.31s; SD=17.38) was in the atypical range (>55s/+1SD), based on the revised criteria, and 64% used longer than 70s (>+2SD) to complete the cognitive-speed task. The average overhead (shift cost) at baseline (M=10.15s; SD=6.97) approached the atypical range (>11s or >+2SD) for healthy adults, based on revised criteria. Among adults with ADHD and SUD, 92.31% responded with longer-than-normal color-form naming times (>55s) and/or larger-than-normal overhead (shift cost) values (>5s) at baseline, when compared to healthy adults in the same age range.

We also compared the AQT color, form and color-form naming and overhead (shift cost) profiles in 42 adults with moderate-to-severe depression and 42 adults with ADHD without depression, selected from among the responders in previously published studies [21,22]. Patients with depression were included in a previously published, double-blind study of the effects of active or sham low-intensity transcranial application of Pulsed Electro Magnetic Fields (T-PEMF) on depression ratings [27,28]. The AQT processing-speed tests were included as T-PEMF outcome measures, but were not reported, and this allowed using the data for comparing response profiles in patients with depression and ADHD without depression. The descriptive statistics for the two diagnostic groups are shown in Table 2.

One-way ANOVA compared processing-speed measures at baseline, before the respective treatments (T-PEMF or methylphenidate), and at endpoint (*ln*), as criteria for normality were rejected. The analyses indicated statistical between-group effects for color (F3, 164=11.37, p<0.0001, η^2=0.17), form (F3, 164=20.25, p<0.0001, η^2=0.27), color-form (F3, 164=26.85, p<0.001, η^2=0.33) and effect sizes were medium. There was also a statistical difference in overhead (shift cost) times (F 3, 164=4.54; p=0.004; η^2=0.08). At baseline before treatment, post hoc analyses showed that color-form naming times were

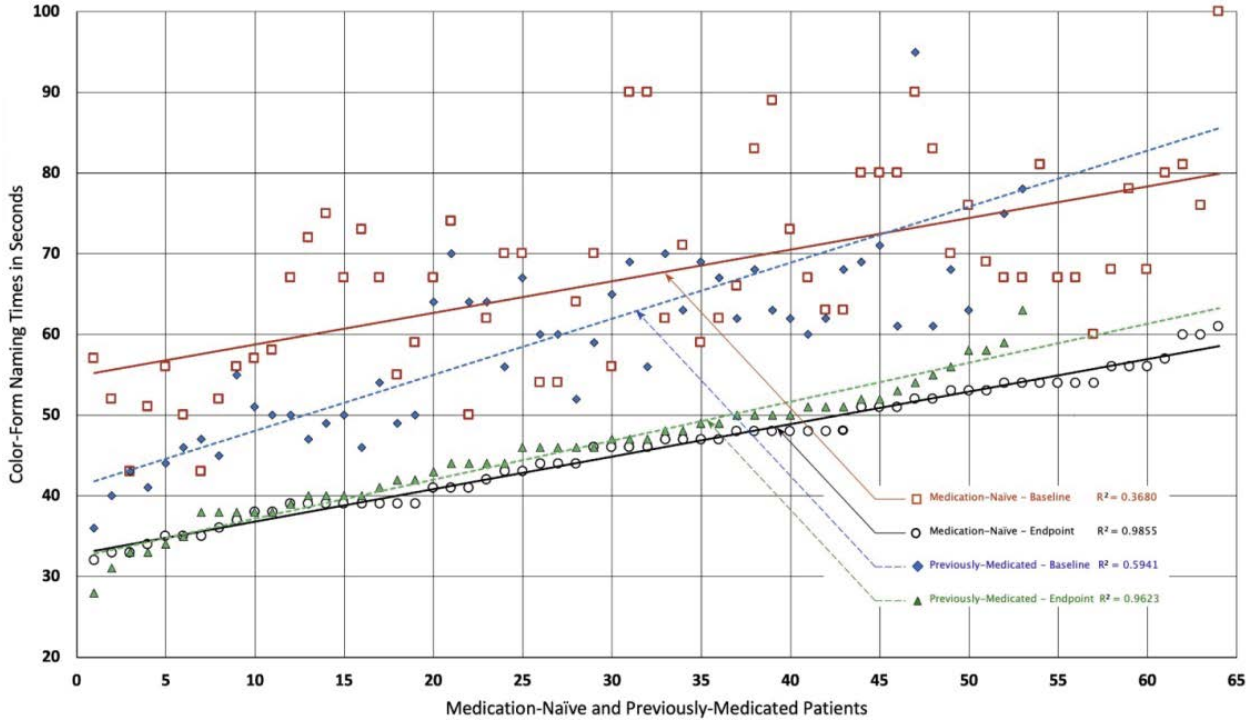

Figure 1. *Plots of individual naming times for 64 medication-naïve and 53 previously-medicated adults with ADHD at baseline without medication and at endpoint after treatment with stimulant medication.*

Table 2. *AQT means, standard deviations, and mean standard error for 42 adults with depression and 42 adults with ADHD without depression pre- and post-treatment.*

	Color	Form	Color-Form	Overhead
	M (SD) MSE	M (SD) MSE	M (SD) MSE	M (SD) MSE
Depression				
Baseline	25.38 (5.31) 0.82	29.52 (5.20) 0.80	55.81(10.21) 1.58	1.31 (7.10) 1.10
Endpoint	23.86 (4.71) 0.73	27.48 (4.41) 0.68	52.02 (8.50) 1.31	1.29 (7.26) 1.12
ADHD				
Baseline	25.90 (6.13) 0.94	29.93 (8.15) 0.92	57.69(12.23) 1.89	5.69 (8.21) 1.27
Endpoint	20.81 (3.83) 0.59	23.19(4.21) 0.65	45.19 (6.88) 1.06	1.24 (4.32) 0.68

longer (Scheffe=4.36; p=0.000) and overhead (shift cost) larger (Scheffe=3.14; p=0.022) in the ADHD than in the depression group. More importantly, overhead (shift cost) values were larger at baseline than at endpoint for the ADHD group (Scheffe=3.14; p=0.022). There was no statistical difference in overhead (shift cost) between baseline and endpoint in the depression group.

Monitoring Methylphenidate Dose Effects

The first study that used the color, form and color-form naming test to obtain quantitative measures of the effects of stimulant medication included 69 medication-naïve adult referrals with probable ADHD [20]. Sixty-four patients, ranging in age from 17 to 55 years, completed the pharmacological treatment and responded to medication. At baseline without medication, the naming time means for color (24.63s) and form (29.50s) were within the average range for healthy adults (<25 s, <30 s, respectively) [2,14,15]. In contrast, the mean for color-form naming (66.69 s) was in the longer-than-average range (>55 s) and overhead (shift cost) (13.00 s) was in the atypical range (>5 s) compared to healthy adults ages 18-55. After treatment, the means for color-form (45.84s) and overhead (shift cost) (3.41 s) were well within the average range (<55 s and <+/-5 s), as compared to healthy adults in the same age range. One-way ANOVA, using *ln* values, indicated statistical difference between the naming times at intake without medication (baseline) and after treatment with stimulant medication (endpoint) for all measures. Effect sizes ranged from medium to large and the average naming time for completing the color-form task was reduced by 31%. The reduction in the overhead (shift cost) also proved significant (t1, 91=8.71; p<0.0000; η^2=0.45) and the average overhead was reduced by 73%. The observed improvements in cognitive speed (color-form) and processing efficiency (overhead) suggested the need for further controlled dose-effect studies in adults with ADHD with the AQT processing-speed tests.

Independent regional studies that used identical methods and procedures monitored the effects of controlled, incremental doses of methylphenidate IR on the AQT processing-speed and overhead (shift cost) measures in 60 patients [21,22]. When the samples in the two studies were combined, 53 patients (88.3%) responded to treatment with methylphenidate. The first test administration (baseline) occurred in the morning, after two days without medication and the second occurred within one-hour after ingesting 8.65/17.39 mg methylphenidate IR (low-dose). The tests were re-administered about 1 hour after the ingestion of a second dose of 8.65/17.39 mg methylphenidate IR (high-dose). Descriptive statistics for the 53 previously-medicated responders to methylphenidate for each test variable and treatment condition are shown in Table 2. At baseline, the means for color, form, and color-form were at the upper limits of the average range (<25, <30, and <55 s, respectively). The mean for the overhead (shift-cost) was also in the average range (<5s) at baseline but the inter-individual variability (SD=8.40) was larger than for healthy adults ages 18-70 (M=2.85; SD=5.52) [15]. With low-dose methylphenidate, the means for color, form, color-form, and overhead (shift cost) were within the average range but the inter-individual variability remained high. At endpoint with high-dose methylphenidate IR, the means for color, form, color-form, and overhead (shift cost) were well within the average range, compared to healthy adults in the same age range and based on the updated criteria (Table 3).

One-way ANOVA indicated significant treatment effects for color (F2, 156=5.08;p<0.007; η^2=0.06), form (F2,156=8.36;p=0.0004; η^2=0.10), and color-form naming (F2, 156=11.20;p=0.00003; η^2=0.13), with effect sizes in the low range. Post hoc analysis for color naming indicated significantly longer naming times without medication than with high-dose methylphenidate (Scheffe=2.98; p<0.01). For form naming, times proved longer

Table 3. *Means and standard deviations for color, form and color form naming times and overhead (shift cost) values for methylphenidate treatment effects by 53 previously-medicated adults with ADHD.*

Treatment	Color	Form	Color-Form	Overhead
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
No medication	25.49 (6.17)	29.38 (8.91)	59.89 (13.91)	4.77 (8.40)
Low-dose	22.23 (5.44)	24.91 (6.55)	51.51 (11.75)	4.00 (8.84)
High-dose	20.81 (3.74)	22.75 (4.12)	45.38 (7.60)	1.81 (3.09)

without medication than with low-dose (Scheffe=2.93; p=0.02) or high-dose methylphenidate (Scheffe3.93; p=0.0006). For color-form combinations, naming times were also significantly longer without medication than with low-dose (Scheffe=2.90; p<0.02) or high-dose methylphenidate (Scheffe=4.71; p=0.00003). Non-parametric analysis of overhead (shift-cost) values, Chi-Square corrected for ties, also indicated statistical differences between treatment conditions (Chi-Square=11.94; p=0.003). The largest overhead values occurred without medication (baseline), second largest with low-dose, and smallest with high-dose methylphenidate IR (endpoint). Twenty-one responders to medication (39.6%) reached maximum treatment effects with low-dose methylphenidate, based on conservatively set criteria that the difference between the color-form naming times for the low-dose and high-dose conditions would be +/-3s or less. At endpoint, overhead (shift cost) values were in the average range (<5s) for the majority of the responders (89%). Individual color-form naming times and linear regression lines for the no medication (baseline), low-dose and high-dose methylphenidate (endpoint) conditions, ranked based on the endpoint measures, are shown in Figure 2.

The AQT processing speed measures have also been used for monitoring the pharmacological treatment of 28 adults with ADHD and Substance Use Disorder (SUD), of which 26 responded to medication [26]. Patients were evaluated in the morning before ingestion of a morning dose of methylphenidate (baseline) and two-three hours later after the ingestion of methylphenidate IR/MR in varying doses ranging from 20 to 216 mg (M=101.43mg), as prescribed by their physicians and approved by medical authorities. At baseline, the means were 31.54s (SD=7.92) for color, 39.08s (SD=10.19) for form, 75.31s (SD=17.38) for color-form, and 10.15s (SD=6.97) for overhead (shift cost) and all measures were in longer-/larger-than-average range. After ingesting methylphenidate, the corresponding means for color 25.00s (SD=5.66) and form 30.23s (SD=7.37) were reduced to the average-normal range. The means for color-form 62.62s (SD=13.97) and overhead (shift cost) 10.50s (SD=9.28) remained in the larger-than average ranges at endpoint. One way ANOVA indicated statistical treatment effects for all measures: color (F1,50=12.82;p=0.001; η(2)=0.20), form (F1,50=13.54; p=0.001; η (2)=0.21), and (F1,50=8.15;p=0.01; η (2)=0.14) but not for overhead (shift cost) (F1,50=0.31; p=0.58). Correlations between measures at baseline and after ingestion of methylphenidate dose (mg) (Spearman's Rho) proved non-significant for color, form and color-form (p>0.05) and methylphenidate dose accounted for less the 1% of the variance in outcomes. In this clinical group, 92% exhibited longer- or larger-than-average or atypical values for two or more of the measures at baseline.

Discussion

As an introduction, we acknowledge that the AQT processing-speed measures have been used primarily in clinical studies of adults with ADHD that were conducted in Scandinavia. The clinical studies were approved by regional authorities in Denmark and Sweden and were carried out in accordance with the Declaration of Helsinki and the EU directive of Good Clinical Practice [29]. The normative data, used as references for the studies reviewed and updated for this review, were first collected in the US with healthy adult speakers of American-English and in Denmark and Sweden with healthy adults in the same age range [1,2]. It is important in this context that no statistical differences have emerged in comparisons of the normative data for English and the Scandinavian languages referenced [1,2]. The similarity in the processing and response measures for color, form and color-form combinations can be attributed to the fact that these languages are of Anglo-Germanic origin and that the syllable lengths are identical in the three languages, with the exception of the multi-syllabic label '*yellow*' used in English [1,2].

In daily practice, the time used for testing, the ease of training allied-health professionals in test administration, and the patient's

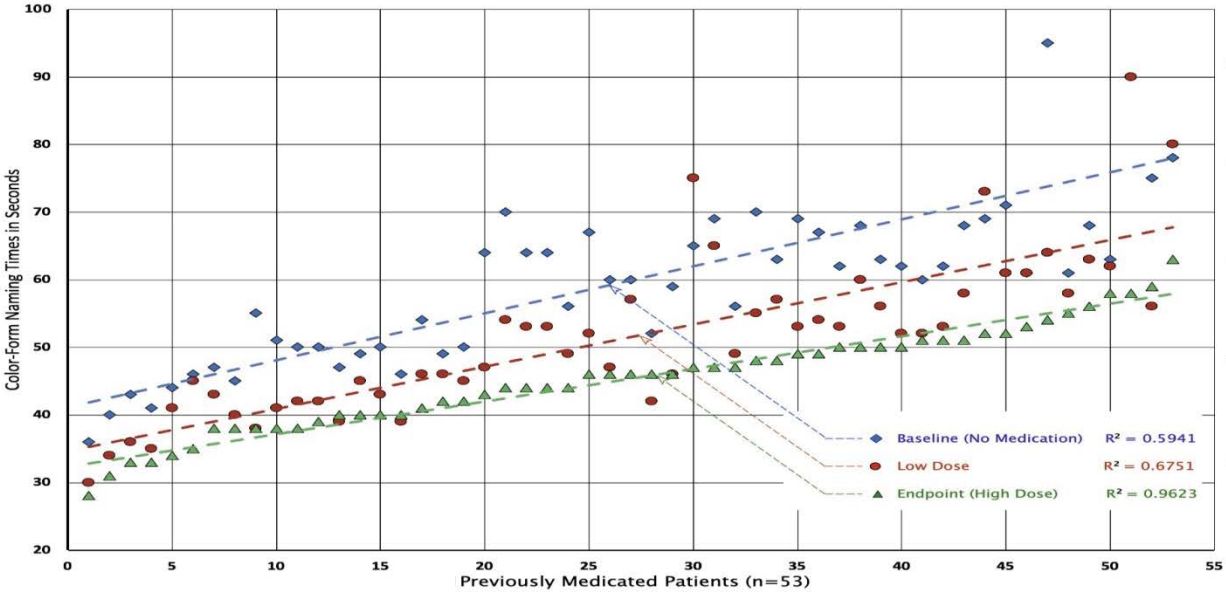

Figure 2. *Plots of individual color-form naming times for 53 previously-medicated adults with ADHD at baseline without medication, with low-dose methylphenidate, and at endpoint with high-dose methylphenidate.*

reactions to the test are important subjective choice factors. The AQT three processing-speed tests can be administered within a short time period of from 5 to 8 minutes and allied-health professionals can readily be trained to administer and record test results. Feedback from patients indicates that they are minimally stressed by responding to the tests after the initial familiarization trial. The statistical characteristics of a test, such as absence of gender bias and acceptable or high test-retest reliability, are among objective factors of importance to clinicians and researchers.

With regard to gender, we have not observed any bias in the responses of healthy adult males and females [1,2,14]. In reports of symptoms associated with ADHD, there have been indications of gender differences, as males appear to exhibit greater levels of impulsivity than females [23,24]. We hypothesized that any gender differences associated with ADHD would occur without medication and that there would be no gender differences after appropriate medication with methylphenidate. In the gender comparison, presented in this review, we observed no statistical differences in cognitive speed (color-form) or efficiency (overhead) at baseline without medication or at endpoint between previously-medicated males and females with ADHD, who participated in published dose-effect studies [21,22]. Because the clinical sample was relatively small and biased in favor of males, we acknowledge that the findings cannot be generalized medication-naïve adults or patients with ADHD symptomatology associated with major comorbidities such as SUD.

In healthy adults, the AQT processing speed measures are associated with high levels of test-retest reliability [1,2]. Among adults with ADHD, the reliability of the color, form and color-form processing-speed measures were not previously tested without medication or after treatment with methylphenidate. For this review, we established the stability of the AQT measures in previously-medicated adults with ADHD, who participated in published, independent studies [21,22]. After treatment with a maximum dose of methylphenidate, the correlation between test-retest measures proved high and similar to that observed in healthy adults [1,2]. Without medication, the test-retest correlations were still in the acceptably high range but they were slightly lower, indicating greater intra-individual response variability. More importantly, the difference between the coefficients of correlation (r) at baseline and endpoint of treatment proved of medium effect size and this is considered to indicate less variability in responding with stimulant medication than without medication. The lower measure of association for the unmedicated condition in adults with ADHD is in line with reports of slower processing speed and increased response variability in children with ADHD [30-32]. The improved stability in responding is considered of clinical and everyday-functional relevance. The response variability in children has been reported to contribute to 17% of the reductions in reading fluency [32] and similar effects on vocational or professional tasks that involve reading should be observable in adults with ADHD.

The pattern of generally longer color-form naming times and larger overhead (shift cost) in adults with ADHD than in healthy age peers was first observed in studies with medication-naïve adults with ADHD from an urban setting in Denmark [20]. This pattern was also found to differentiate healthy adults and adults with ADHD and adult psychiatric referrals with and without ADHD in the same setting [25,33]. Recently, the same processing-speed and overhead pattern was observed in independent studies in Sweden of previously-medicated adults with ADHD and adults ADHD with SUD [21,22,26]. The pattern also differentiated adults with ADHD without depression and adults with depression without ADHD, as reported in this review.

The strength, with which the combination of average color and form naming times and longer/larger-than-average color-form and overhead (shift cost) times (s) differentiates between clinical groups with ADHD diagnoses, is not uniform. It seems to vary depending on factors related to the number and types of comorbidities and whether patients were medication-naïve or previously medicated. The sensitivity of the differentiating characteristics in the cognitive speed (color-form) and processing efficiency (overhead) profiles of adults with ADHD appears highest in adults with ADHD and comorbid SUD (92%) and only slightly lower in medication-naïve adults with ADHD (91% and 89%) [25,26]. The characteristic response profile shows slightly lower but acceptable levels of sensitivity for previously-medicated adults with ADHD (85% and 83 %) [21,22]. The observation that the sensitivity of using the AQT response profiles as indices of ADHD was lowest in previously-medicated adults with ADHD agrees with results from research that compared cortical-activation patterns in stimulant-naïve and previously-medicated children and adults [34]. During the performance of tasks that focus on attention and interference control, all but one study reviewed reported attenuation of abnormal activation in cortical areas after long-term stimulant medication. The regions, in which attenuation occurred, included the prefrontal, temporal, parietal, and occipital regions of the cortex [32]. Of these, the temporal-parietal and occipital regions were shown to be activated bilaterally, with concurrent deactivation of the prefrontal regions, during the performance of the color-form naming task in rCBF [1,2] and f-MRI.

When comparing the processing-speed profiles of adults with ADHD, who are medication naïve or who have received stimulant medication long-term, there appear to be remarkable differences [20-22]. Comparison of the average times reported for the two groups for the perceptual-speed measures, 24.63s and 25.49 s for color and 29.50 s and 29.38 s, indicate no differences between groups at baseline without medication. In contrast, the average times for the color-form measures at baseline (66.69s and 59.89s, respectively) indicate that naming times are about 6s (+1SD) longer for the medication-naïve than for the previously-medicated adults with ADHD. At baseline, shift costs were also larger for the medication-naïve than for the previously-medicated group (13.00 s and 7.43 s, respectively) and differed by more than +/-6s (+/-1SD). The lower baseline values for cognitive speed (color-form) and processing efficiency (shift cost) for adults with ADHD after

prolonged use of methylphenidate, are in line with observations from functional f-MRI studies of children and adolescents after stimulant medication use [32]. Several of the studies reviewed by the authors found that stimulant medication reduced the levels of abnormal activation in the temporal, parietal and occipital lobes, that is, the same cortical regions of bilateral activation in adults with ADHD during the performance of color-form naming [1,2]. The average processing-speed times reported for the medication-naïve and previously-medicated adults with ADHD at endpoint, after stabilization with stimulant medication, did not differ for any of the measures, suggesting that the groups were equally responsive to treatment with methylphenidate. The findings suggest that the processing-speed measures (color, form and color-form) and the calculated overhead (shift cost) may be relevant for use in daily psychiatric or primary practice. For both medication-naïve and previously-medicated adults with ADHD, these quantitative measures may complement behavioral ratings or screening tests used at intake or to quantify the effects of receiving stimulant medication.

Conclusion

We acknowledge that heterogeneity in genetic, environmental, and neuropsychiatric factors may have influenced the lack of gender bias and the sensitivity and reliability levels of the processing-speed and overhead measures, as reported here. The currently available evidence of differential AQT perceptual-(color, form) and cognitive-speed (color-form) and efficiency (overhead) response patterns, however, appears to support the use of the measures during the initial screening of adults with probable ADHD. This seems to be the case especially for screening medication-naïve adults with suspected ADHD or adults with Substance Use Disorder (SUD) and therefore potentially with ADHD.

When we evaluated the ability of the AQT measures to monitor the effects of controlled, incremental doses of methylphenidate, the outcomes of the independently-conducted clinical studies proved similar [21,22]. For this review, we combined the results of the two studies and observed statistical differences in perceptual and cognitive speed and overhead (shift cost) between the no-medication, low dose and high-dose methylphenidate IR conditions. For the perceptual-speed measures (color, form), the statistical treatment effects occurred only between the no-medication and high-dose methylphenidate conditions. For the measures of cognitive speed (color-form), there was an increase in speed between the no-medication and the low-dose methylphenidate and between the no-medication and high-dose methylphenidate conditions. The fact that dose-optimization seemed to be established with low-dose methylphenidate for 21 of the patients with ADHD (39.6%) appears of greater relevance. This finding suggests that the measures can establish a minimum, but optimum, level of medication at which a larger dose would not results in substantial changes in processing speed or efficiency. In summary, the findings suggest that the AQT processing-speed and overhead measures may prove clinically useful to:

a) Monitor responsiveness to stimulant or alternative medication in adults with ADHD
b) Identify non-responders to the specific medication
c) Establish optimum dose levels
d) Determining whether medication may be safely discontinued after long-term use and without recurrence of the ADHD symptomatology.

Within the limitations stated above, and discussed in the published studies, the statistical characteristics of the AQT processing-speed and efficiency measures, when used for adults with probable or established ADHD, indicate adequate concurrent validity with commonly used neuropsychological tests [18,19]. The test-retest reliability in adults with ADHD appears lower without medication, indicating intra-individual response variability, and higher after treatment with stimulant medication, when responses have become more stable. In healthy adults, there are minimal effects of aging on processing speed and there is no evidence of gender bias [1,2]. The preliminary comparison of gender differences, reported in this review, suggests no differences between male and female adults with ADHD either without medication or after treatment with optimum doses of methylphenidate. Patterns in the processing-speed and overhead measures indicate that longer-than-average naming times and larger-than-average overhead can differentiate healthy adults and adults with ADHD and adults with ADHD without and with substance use disorder or with depression, as reported here. This pattern appears to show the highest sensitivity in adults with ADHD and comorbid substance disorder and to show slightly lower sensitivity levels with decreases in the severity of the ADHD symptomatology and after long-term stimulant medication. The studies reviewed also indicate that the processing-speed and overhead (shift cost) time values decreased incrementally with controlled doses of methylphenidate and were within the average range at dose optimization for both medication-naïve and previously-medicated adults with ADHD. The gains in cognitive speed (color-form) and overhead values (shift cost) with stimulant medication were similar for stimulant-medication naïve and previously-medicated adults with ADHD and more limited for adults with ADHD and substance abuse disorder. We acknowledge that the findings, reported in this review, would benefit from independent clinical validation with adults with ADHD, who are diagnosed and treated within different medical systems and cultures and who speak languages other than Danish and Swedish.

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