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Differentiating depression and ADHD without depression in adults with processing-speed measures

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Original Article

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Abstract

Objective: We evaluated processing-speed and shift-cost measures in adults with depression or attention-deficit hyperactivity disorder (ADHD) and monitored the effects of treatment. We hypothesised that cognitive-speed and shift-cost measures might differentiate diagnostic groups. *Methods:* Colour, form, and colour–form stimuli were used to measure naming times. The shift costs were calculated as colour–form-naming time minus the sum of colour- and form-naming times. Measurements were done at baseline and end point for 42 adults with depression and 42 with ADHD without depression. Patients with depression were treated with transcranial pulsed electromagnetic fields and patients with ADHD with methylphenidate immediate release. *Results:* During depression treatment, reductions in naming times were recorded weekly. One-way analysis of variance indicated statistical between-group differences, with effect sizes in the medium range for form and colour–form. In both groups, naming times were longer before than after treatment. For the ADHD group, shift costs exceeded the average–normal range at baseline but were in the average–normal range after stabilisation with stimulant medication. For the depression group, shift costs were in the average–normal range at baseline and after treatment. Baseline colour–form-naming times predicted reductions in naming times for both groups, with the largest effect size and index of forecasting efficiency for the ADHD group. *Conclusions:* The cognitive-processing-speed (colour–form) and shift-cost measures before treatment proved most sensitive in differentiating patients with depression and ADHD. Reductions in naming times for the depression group were suggested to reflect improved psychomotor skills rather than improved cognitive control.

Significant outcomes

Shift costs for depression were in the average range for healthy adults at baseline and remained unchanged with treatment.

The largest statistical difference between the depression and ADHD groups occurred for shift costs at baseline, which were larger in the ADHD group.

The processing-speed profile for adults with depression conformed to an additive model in which the colour plus form times s equalled the time for colour–form ±5 s.

Limitations

The groups with major depressive disorders and with ADHD without depression were not matched one-on-one for age or gender.

A clinical group with major depression and comorbid ADHD and a matching group of healthy adult controls were not included in the study.

Findings cannot be extended to patients with depression in general, due to the selection of patients with treatment-resistant major depression for the study.

Introduction

In psychiatric practice, research suggests that for patients with a diagnosis of attention deficit hyperactivity disorder (ADHD), comorbid depression should not only be considered a possibility, but that depressive symptoms may have an additive effect on neurocognitive impairments (Barkley & Brown, 2008; Larochette et al., 2011; McIntosh et al., 2009). In the same vein, comorbid ADHD should be considered in patients with depression, since as many as 80% of adults with ADHD present with at least one neuropsychiatric disorder, most commonly in the form of

depression, reported to occur between 20% and 50% of patients with ADHD (Katzman et al., 2017). In depression, cognitive dysfunction is prominent within domains such as verbal and visual memory, executive functions, psychomotor skills, and attention, and the impairments are not always responsive to pharmacotherapy and may in part persist with clinical remission (Gonda et al., 2015). In clinical practice, it can be difficult to separate, which cognitive domains may be affected in patients with depression, and the presence of ADHD symptomatology can easily be overlooked due to more alarming mood symptoms (Katzman et al., 2017). Among individuals with ADHD, cognitive deficits that affect the domains of attention, working memory, and set shifting, which comprise the central executive, and processing-speed deficits, are considered diagnostic hallmarks (Weigard & Huang-Pollock, 2017). Persistent cognitive dysfunction after treatment for either ADHD or severe depression can have negative impacts on a variety of daily, social, and work-related functions (Katzman et al., 2017). There appears to be a need for the identification of simple cognitive tests that can be used in everyday clinical practice to monitor and predict treatment effects and identify non-responders among patients with depression. These concerns prompted this study in which a quick test of cognitive speed (AQT; Wiig et al., 2002; Wiig et al., 2005), which probes perceptual- and cognitive-speed and processing efficiency, was administered to adults with depression and ADHD without depression.

Processing-speed tests have been used extensively in clinical research of ADHD symptomatology in children and adults (Ryan et al., 2017; Wiig et al., 2002). The additive effects of depression for adults with ADHD have been evaluated by comparing the processing speed and verbal recall in adults with ADHD, with ADHD and elevated depression symptoms, and with depression symptoms without ADHD (Larochette et al., 2011). Findings indicated that the group with ADHD and comorbid depression performed worse on processing-speed tasks than either the ADHD or depression groups. The processing-speed test used in this study contains two single-dimension processing-speed tests, colour and form naming, that measure perceptual speed (reactive attention) and reflect reaction and retrieval and response time (Wiig et al., 2002; Wiig et al., 2005). It also features a dual-dimension naming test, with combined colour–form naming, which measures cognitive speed (active attention) and reflects the proficiency in controlling the added demands on attention, working memory, and cognitive control. In addition, it features a derived measure of shift costs that reflects processing efficiency calculated as colour–form-naming time minus the sum of colour- and form-naming times. The design of the AQT is, at first glance, a variant of the Stroop Color–Word test, but the relatively low correlation between the Stroop interference T-scores and AQT processing-speed measures ($r = -0.31$; $p = 0.049$) points to the differences in the underlying constructs (Fleck et al., 2015). This is reflected in neuroimaging (regional Cerebral Blood Flow) during colour–form naming that consistently indicates bilateral temporal–parietal activation with concurrent deactivation in the prefrontal areas (Wiig et al., 2002; Wiig et al., 2005; Wiig et al., 2009). The areas activated have been associated with the central executive attentional and working memory systems and with cognitive control (Baddeley et al., 1991; Berryhill et al., 2011; Downing, 2000; Esterman et al., 2009). The patterns of activation and functional systems involved suggested that AQT might be used as a complement in clinical assessments of neuropsychiatric disorders that affect executive functioning. Concurrent validity studies provided further support for AQT colour–form naming as a complementary test of aspects of cognition, including attention, working memory, and set shifting (Fleck et al., 2015; Nielsen et al., 2007). Thus, one study of consecutively admitted patients for neuropsychiatric evaluation with subsequent International Classification of Diseases, 10th Revision (ICD-10) diagnoses of mild to moderate dementia, mild cognitive impairment, and affective disorders indicated negative correlations with large effect sizes between AQT colour–form naming and WAIS-III Performance IQ and MMSE. A second study of 40 neurotypical adults indicated a negative association, of moderate effect size, between AQT colour–form-naming times and Montreal Cognitive Assessment scores (Fleck et al., 2015).

The AQTs have been used in clinical research of adults with a variety of neurocognitive disorders, among them patients with Alzheimer's disease (AD), dementia with Lewy bodies, ADHD, and other neuropsychiatric conditions (Andersson et al., 2007; Nielsen et al., 2004; Palmqvist et al., 2010; Nielsen & Wiig, 2011b; Nielsen & Wiig, 2013). It has also been used to assess the stability of responses to medication in patients with AD and to monitor the effects of incremental doses of methylphenidate in adults with ADHD (Wiig et al., 2010; Nielsen et al., 2017; Magell et al., 2018). This research suggested different cognitive-speed and processing-efficiency (shift-cost) patterns for healthy adults, adults with Alzheimer's dementia, and adults with ADHD of the combined type. In adults with AD, naming times proved longer than for healthy peers of their age and cognitive speed deteriorated with the progression of the disease, whereas shift costs were within the average range for healthy adults (Wiig et al., 2009; Palmqvist et al., 2010). In contrast, among adults with ADHD, for 80–90% of patients, colour–form processing and naming times proved generally longer and shift costs larger compared to healthy peers of their age (Nielsen & Wiig, 2011b; Nielsen & Wiig, 2013; Nielsen et al., 2017; Magell et al., 2018; Wiig & Nielsen, 2012). Dose–effect studies further indicated that AQT can identify incremental reductions in colour–form naming and shift costs with controlled increases in methylphenidate immediate release (IR; Nielsen et al., 2017; Magell et al., 2018). These studies indicated that cognitive speed and shift costs were normalised with optimum doses of methylphenidate in 90% or more of patients with ADHD.

Previous studies that used the AQT processing-speed tests, included patients with depression or ADHD with comorbid depression (Nielsen et al., 2007; Nielsen & Wiig, 2011b). However, this is the first study to focus specifically on the use of AQT to assess processing-speed and shift-cost patterns in a sample of treatment-resistant depressed patients before, during, and after treatment. AQT was administered but not reported in a previous, randomised controlled trial that focused on the outcomes of using low-intensity transcranial application of pulsed electromagnetic fields (T-PEMF) for patients with antidepressant-resistant depression. The main outcomes indicated a superior antidepressant effect on depression ratings with active T-PEMF treatment, with 61.0% in remission in the active T-PEMF group versus 33.9% in the sham treated group at end point. For remission, the rates were 33.9% versus 4.1% at end point. This has been reported in two previous publications (Martiny et al., 2010; Bech et al., 2011). Because the processing-speed data were not explicitly explored in those studies, they were used in this study to compare AQT processing-speed response patterns and profiles in adults with depression and with ADHD without depression.

The specific aims of this study were to (a) evaluate the usability of the processing-speed measures with severely depressed patients; (b) assess and compare the relative degree of impairments related

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to attention, working memory, and set shifting in patients with depression and patients with ADHD without depression; and (c) identify specific processing-speed or shift-cost measures, which might differentiate patients with depression from patients with ADHD without depression. One hypothesis was that before treatment (baseline), the cognitive-speed (colour–form) measures would reflect slower than average processing speed in both clinical groups compared to normative data for healthy adults in the same age range. The second was that after specific treatment of depression or ADHD, the cognitive-speed measures would be normalised to within the average range compared to data for healthy adults in the same age range. The third was that the processing-efficiency (shift-cost) measures for the depression group would be within the average range at baseline and after treatment, whereas the shift costs in adults with ADHD would be larger than average at baseline but normalised after treatment with methylphenidate.

Materials and methods

Participants

Patients with treatment-resistant depression were referred from specialists in psychiatry and from open psychiatric wards during a 3-year period. Patients, who met criteria for inclusion, were treated at a psychiatric specialist practice or a psychiatric research unit, both located in the Greater Copenhagen area. Inclusion criteria were (a) age above 18, (b) treatment resistance corresponding to a score of 3 or above on the Sackeim criteria (Sackeim, 2001), (c) major depression according to *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (*DSM-IV*), as assessed by the Mini International Neuropsychiatric Interview (M.I.N.I.) instrument (Sheehan et al., 1998), (d) a score of 13 or above on the 17-item version of the Hamilton Depression Rating Scale (HAM-D; Bech et al., 2014; Hamilton, 1960; Martiny et al., 2013), and (e) unchanged psychotropic medication for the previous 4 weeks. Exclusion criteria were (a) suicidal ideation corresponding to a score of 2 or above on the HAM-D item 3, (b) alcohol or drugs abuse during the last year, (c) previously having received T-PEMF treatment, (d) any known antisocial, borderline, schizotypal, or psychotic disorders or dementia, and (e) any foreseeable reason not to be able to comply with a minimum of 80% of the daily treatments and weekly assessments. For women of reproductive age, pregnancy or insufficient contraception or lactation were causes for exclusion.

The diagnoses of major depression and comorbid conditions were made using M.I.N.I. to secure that patients, at inclusion, which fulfilled the diagnostic criteria for major depression, and to assess the level of comorbidity. Self-assessed levels of depression were obtained by the major depression inventory (Bech et al., 2015), which covers the *DSM-IV* criteria. The level of treatment resistance was assessed by the antidepressant treatment history form (Sackeim, 2001) with a score of 3 or above required for inclusion with the currently used antidepressant drugs (range 0–5, with 5 signifying the highest level of treatment resistance). Response to treatment was defined as a reduction of 50% or more on the HAM-D_{17} scale, and it was used as the primary depression outcome scale with patients being assessed once weekly for 5 weeks. The Hamilton 6-item subscale (HAM-D_6; Martiny et al., 2013) and the melancholia scale (MES; Bech et al., 2014) evaluated secondary depression outcomes. The UKU (Udvalget for Kliniske Undersøgelser) scale evaluated the side effects (Lingjaerde et al., 1987).

For patients with depression, the number of participants for the original study (Martiny et al., 2010) was determined on the assumption that active treatment with T-PEMF would reduce the HAM-D score with 12.5 points from baseline to end point and that sham treatment with T-PEMF would reduce the score with 9 points. With a power of 80 %, an expected standard deviation (SD) of 4 and a type I error of 5 %, the number of participants was calculated to at least 44. The intention-to-treat principle was applied and all randomised patients (N = 50) were included in the analyses and 47 patients were evaluated with the AQT at baseline. In the present study, we excluded one outlier from the T-PEMF and one from the sham treatment group, each with atypically long colour–form-naming times that exceeded 100 s. Of the remaining 45 patients, who were evaluated with AQT at baseline, we included the 42 patients that completed at least four assessments.

The study was carried out in accordance with the Declaration of Helsinki and the EU directive of Good Clinical Practice and was monitored continually throughout the study period (Encorium Denmark, Hørsholm, Denmark). The local Committee on Biomedical Research Ethics and the Danish Central Data Register approved the study. Patients were given information about the study by following the guidelines for inclusion procedures set out by the Committee on Biomedical Research Ethics. All patients signed an informed consent after having received oral and written information concerning the study.

Patients with ADHD were referred by primary physicians or specialists in psychiatry to regional psychiatric hospitals in Västervik and Wäxsjö, Kalmar Region, Sweden, during a 3-year period. Prerequisites for inclusion in the study were that patients must have (a) Swedish as their primary/native language; (b) IQ at 80 or above; (c) a diagnosis of ADHD according to Swedish standards; (d) no substance abuse at the time of study; (e) no evidence of antisocial, borderline, schizotypal, or psychotic disorders or dementia; (f) no concomitant diagnosis of depression; and (g) no or well-controlled diabetes or thyroid dysfunction. The original diagnoses of ADHD were obtained by assessments with behavioural rating scales, including ADHD-Adult ADHD Self Report Scale (ASRS)-v.1.1 and Brown's Attention Deficit Disorder (ADD) scales (Silverstein et al., 2018; Rucklidge & Tannock, 2002) and psychological evaluations that included the WAIS-IV measures of verbal and non-verbal intelligence, working memory, performance speed (Theiling & Petermann, 2016), and test of variables of attention (Greenberg & Waldman, 1993) were also administered to the majority of the participants.

We identified 42 patients, ranging in age between 17 and 60 years, all of whom were diagnosed with ADHD (F90.0B) without comorbid depression, and they served as participants in this study.

Because the participants were of legal age, the diagnostic process did not include relatives. Psychiatric interviews at the time of the study indicated that none of these, previously medicated patients showed actual evidence of classical depression. The patients participated in earlier published, incrementally controlled methylphenidate dose–effect monitoring studies (Nielsen et al., 2017; Magell et al., 2018). Patients in the depression and ADHD groups were not matched for gender or age, as studies have indicated no statistical differences between healthy men and women and minimal increases in processing speed of 1 s per decade till age 60 years and 1 s per 7 years between ages 61 and 85 years (Jacobson et al., 2004; Wiig et al., 2007). The original methylphenidate dose-monitoring studies were carried out in accordance

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with the Declaration of Helsinki and the EU directive of Good Clinical Practice. Authorities in the Region Kronoberg approved the studies. After receiving oral or written information about the study, all participants with ADHD signed an informed consent, in accordance with the Declaration of Helsinki.

Processing-speed measures

The AQT colour, form, and colour–form combination processing-speed tests, each with 40 visual stimuli, consisting of four randomised coloured squares (*black*, *blue*, *red*, and *yellow*), black geometric forms (*circle*, *line*, *square*, and *triangle*), or combinations of the colours and forms, were administered to all participants by the attending psychiatrists. Short, untimed familiarisation trials with colours, forms, and colour–form combinations were administered to establish adequacy and consistency in naming the experimental test stimuli. Subsequently, the tests were administered in the prescribed order, first colour, then form, and then colour–form. Before each test, participants were instructed to name the visual stimuli as fast and accurately as possible, proceeding line-by-line from left to right as in reading. The total time (s) for naming the 40 stimuli in each test was measured digitally, beginning immediately after the instruction to start and ending with the naming of the last stimulus on each test plate. In the patients with treatment-resistant depression, the AQT test was administered approximately 1 h after T-PEMF treatment.

The processing-speed tests have been norm- and criterion-referenced with healthy adolescents and adults in the age range from 15 to 85 years. They show a high degree of test–retest reliability with intraclass correlations (r) of .91 for colour, .92 for form, and .95 for colour–form naming. Criterion-referenced cut-off times (s), using the naming time distributions for age cohorts of healthy adults, have been established for the average (<+1.0 SD of the mean), slower than average (between +1.0 and +2.0 SDs), and atypical naming time ranges and shift costs (<+2 SD). The cut-off criteria ranges are identical for Danish and Swedish, due to the identical syllable length of the stimulus labels. There has been no evidence of gender bias or effects on learning or habituation with repeated trials (i.e. over 10 min) and cognitive speed has been observed to decline by about 1 s per decade under age 60 and about 1 s/7 years above age 60 years in healthy adults.

The design of the tests allows for the calculation of shift cost, which assesses processing efficiency. Shift cost is calculated by using the formula [CF – (C + F)], and this measure has been established to be less than ±5 s in healthy adults. Among adults with AD, shift costs generally fall within the limits for average performance, but the overall speed of naming deteriorates for all tasks with progression of the disease. In adults with ADHD in the age range below 60 years, the colour–form and shift costs are generally longer/larger than average (i.e. >55 s and >±5 s, respectively). With methylphenidate, the processing speed can generally be normalised to <25 s for colour, <30 s for form, and <55 s for colour–form naming, and shift costs to <±5 s.

Treatment procedures

For patients with depression, treatment was designed as a double-blind parallel randomised controlled trial and patients were assigned to either active or sham T-PEMF treatment. The psychopharmacological treatment (antidepressants, mood stabilisers, antipsychotics, tranquilisers, and hypnotics), unchanged during the previous 4 weeks, was maintained at the same dosage level throughout the study. T-PEMF treatment was self-administered by patients on all weekdays for 5 weeks, but with supervision from health personnel at the psychiatric research unit or the psychiatric specialist practice. The T-PEMF condition (sham or active) was blinded for both researchers and patients. The original study procedures and primary outcomes were reported in detail in an earlier publication. Trained health staff secured an accurate activation of the generator and compliance with the 30 min daily session of supervised treatment. Zopiclone, with a maximum daily dosage of 7.5 mg, was permitted to treat emergent sleep disturbances. No other change in ongoing psychopharmacological treatment was allowed.

For patients with ADHD, controlled treatment with increasing doses of methylphenidate IR was administered during scheduled annual reviews, and psychiatrists administered the tests over a period of 3–4 days. After 2 days (weekend) without the prior prescribed methylphenidate medication, a processing-speed baseline was obtained. This was followed by the ingestion of two equal doses of IR methylphenidate hydrochloride tablets, equivalent to 8.79/17.39 mg methylphenidate (Medikinet IR). Processing speed was re-assessed after the ingestion of the first methylphenidate dose (low-dose condition) and then after an added dose of methylphenidate (high-dose condition) administered at about 1-h intervals. The measurements obtained at baseline and at end point, after the ingestion of the equivalent of 17.39/34.78 mg methylphenidate, were used in the present study. The dose-monitoring procedures and incremental treatment outcomes were described in greater detail in the earlier published studies (Nielsen et al., 2017; Magell et al., 2018).

Statistical analyses

The analysis of the weekly colour–form-naming times and shift costs for the active T-PEMF and sham treatment groups with depression used a mixed model. It included baseline AQT naming times, week, treatment group, the interaction of week and treatment group, and (for the exploratory analyses) depression scores as covariates. The interaction in the model tested the identity of the two treatment groups. The mixed model was also used to test for any predictive values of AQT baseline naming times on end point depression scores (visits 5 or 6). Correlations were obtained by the Spearman rank method due to the lack of normality of the naming times. Statistical significance for rejection of the null hypothesis was set at a $p < 0.05$. All analyses were performed using the SAS 9.4 software.

Baseline and post-treatment processing-speed times and shift costs in each diagnostic group, depression or ADHD, were compared by one-way analysis of variance (ANOVA) with *post hoc* analyses (Scheffe), following log normal (ln) transformation, if criteria for normality were rejected (Shapiro–Wilk W). Correlations (Spearman r) were obtained to assess the association between variables, when distributions did not meet the criteria for normality. The level of statistical difference for rejecting the null hypothesis for main effects was set at $p < 0.01$ to avoid bias. For the *post hoc* analysis, statistical differences were accepted at $p < 0.05$. The analyses were performed using the SAS 9.4 or StatPlus: macPro v5.9.92 (Analyst Soft Inc., Walnut, CA, USA) software.

Results

Sociodemographics

ADHD patients ($n = 42$) had a mean age of 34.2 (SD = 12.3) years with 38.1% females (16/42). All patients fulfilled the *ICD-10*

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Table 1. Mean AQT naming time and overhead (s) at baseline and following treatment by group, T-PEMF active or sham ($n = 47$)

Week	Colour mean (SD)	Form mean (SD)	C-F mean (SD)	Shift cost* mean (SD)
Baseline				
Active	27.0 (7.6)	33.2 (8.6)	61.4 (17.1)	1.2 (7.1)
Sham	26.9 (5.2)	32.4 (7.0)	60.9 (13.1)	1.6 (8.1)
Week 1				
active	26.1 (8.1)	30.9 (8.4)	61.6 (19.3)	4.6 (8.0)
sham	25.4 (3.6)	30.9 (5.6)	58.4 (11.5)	2.0 (8.5)
Week 2				
active	26.0 (5.1)	30.0 (6.4)	57.4 (17.6)	1.5 (10.5)
Sham	23.9 (4.6)	29.3 (5.8)	55.0 (10.5)	1.7 (6.5)
Week 3				
active	25.8 (7.1)	28.4 (7.8)	58.3 (17.3)	4.1 (9.6)
sham	23.7 (4.0)	28.6 (5.1)	54.4 (10.6)	2.1 (7.4)
Week 4				
active	25.8 (6.7)	28.5 (6.2)	59.3 (17.3)	4.9 (8.1)
sham	22.7 (4.0)	28.0 (5.5)	54.4 (10.6)	3.8 (7.6)
Week 5				
active	25.0 (7.3)	28.1 (6.6)	55.9 (18.3)	2.8 (7.9)
sham	24.1 (4.4)	28.4 (5.3)	53.1 (10.1)	0.6 (7.5)

*Shift cost = [colour–form − (colour + form)] in seconds
Abbreviation: C-F = colour–form

diagnostic criteria for ADHD (F90.0), four patients also fulfilled the *ICD-10* criteria for major depressive disorder, single episode, mild (F32.0), and one patient also fulfilled the *ICD-10* criteria for generalised anxiety disorder (F41.1). The ASRS version 1.1 A *and* B baseline score was 42.7 (12.9). The treatment-resistant depressed patients ($n = 42$) had a mean age of 52.4 (SD = 11.3) years with 69.0 % females, a current duration of depressive episode of 50.6 (SD = 98) months, and a baseline HAM-D_{17} score of 20.9 (SD = 3.7). All treatment-resistant patients were in actual treatment with one or more antidepressant drugs (Martiny et al., 2010). There was no statistically significant relation between AQT outcomes (naming times and shift costs) and duration of actual depressive episode.

Depression treatment outcomes

We first performed statistical analyses of the processing-speed time measures (s) obtained weekly by patients with depression during active T-PEMF or sham treatment. The colour, form, and colour–form tests were administered during the daily treatment sessions for each week and naming times and shift costs were recorded. Table 1 shows the mean AQT naming times at baseline and all the following visits for each treatment group with SDs. Mixed model analysis results for colour ($F_{41,\ 6} = 6.49$; $p = 0.0146$), form ($F_{42,\ 0} = 17.20$; $p = 0.0002$), and colour–form-naming times ($F_{40,\ 9} = 27.41$; $p < 0.0001$) diminished moderately and indicated statistical differences after each week of treatment. In contrast, shift costs were unchanged with time (visits) ($F_{42,\ 2} = 0.00$; $p = 0.97$) and showed considerable inter-individual variability but remained within the normal range (<±5 s) throughout treatment. When entering depression scores (HAM-D_{17}, HAM-D_6, or MES) into the full model, there was a statistical effect on all naming-time measures for the three tasks. The effect was largest for the HAM-D_6 on the colour–form naming task with a parameter estimate of 0.74 ($F_{135} = 19.29$, $p < 0.0001$). The interpretation is that an increase in one point on the HAM-D_6 scale corresponded to an increase in naming speed on the colour–form task of 0.74 s at any visit.

Subsequently, we compared naming times and shift costs at baseline and post-treatment (end point) for the active T-PEMF ($n = 22$) and sham ($n = 20$) treatment groups with depression. This analysis used patients with a baseline AQT colour–form-naming time less than 100 s or who had completed more than 4 visits. Table 2 shows the means and SDs for colour, form, and colour–form naming and shift costs (s) for Group A, receiving T-PEMF ($n = 22$), and Group B, receiving sham treatment ($n = 20$) before and after 5 or 6 weeks of daily treatments. At baseline, the means for the two treatment groups (active and sham) were slightly above the average range for healthy adults for colour and form (i.e. >25 and 30 s, respectively), and for the colour–form combinations the mean approached the upper limit of the average range (i.e. 55–60 s) (Wiig et al., 2002; Wiig et al., 2005). After treatment all processing-speed measures were within the average–normal range (i.e. colour <25 s, form <30 s, and colour–form <55 s) and shift costs were well within the average range at baseline and after treatment (i.e. <±5 s) (Nielsen & Wiig, 2011a).

With normality accepted for all distributions (Shapiro–Wilks *W*), one-way ANOVA, using naming times in seconds, indicated no statistical differences between groups at the *a priori* set level of significance ($p < 0.01$) for colour ($F_{3,\ 80} = 1.42$; $p = 0.24$; $\eta^2 = 0.05$), form ($F_{3,\ 80} = 3.48$; $p = 0.02$; $\eta^2 = 0.12$), colour–form naming ($F_{3,\ 80} = 1.91$; $p = 0.14$; $\eta^2 = 0.07$), or shift cost ($F_{3,\ 80} = 0.88$; $p = 0.46$; $\eta^2 = 0.03$) and effect sizes were generally low. *Post hoc* analysis indicated no statistical between-group treatment effects between groups at baseline or end point for colour, form, colour–form naming or shift costs, and the results were accepted to indicate that the two treatment groups could be combined for further analyses.

Comparing depression and ADHD

After combining the two depression groups (Groups A and B), there were 42 adults with major depression and 42 with ADHD without depression. Table 3 shows the means, SDs, mean standard errors (MSEs) for colour, form, colour–form naming, and shift costs before and after the respective treatments. At baseline, the means for colour and form for both clinical groups were slightly above or at the upper limits of the average range, compared to healthy adults in the same age range (i.e. >25 and >30 s, respectively). The mean for colour–form combinations was within the average range for the depression group but slightly above the average–normal range for the ADHD group (i.e. >55 s). Shift costs were in the average–normal range (<±5 s) in the clinical group with depression but exceeded the average range in the group with ADHD without depression. At end point, the naming time measures for both diagnostic groups (colour, form, and colour–form) were within the average–normal range (i.e. <25, <30, and <55 s, respectively). Shift costs for patients with depression remained well within the average range post-treatment, whereas the average shift costs for adults with ADHD were reduced from the upper limits of the average–normal range at baseline to well within the average range after optimum treatment with methylphenidate.

With normality rejected for several of the distributions (Shapiro–Wilks *W*), naming times (s) were submitted to log

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Table 2. Means, standard deviations, and mean standard error (MSE) for adults with depression, receiving active T-PEMF treatment (Group A) ($n = 22$) or sham T-PEMF (Group B) ($n = 20$)

Group	A. Baseline	End point	B. Baseline	End point
variable	M (SD) MSE	M (SD) MSE	M (SD) MSE	M (SD) MSE
Colour	26.50 (5.33) 1.14	23.77 (4.23) 0.90	24.15 (5.14) 1.15	23.95 (5.31) 1.19
Form	31.27 (4.84) 1.03	27.64 (3.74) 0.80	27.60 (4.99) 1.12	24.89 (5.15) 1.15
C-f	57.82 (9.41) 2.00	51.45 (6.49) 1.38	53.60 (10.85)2.45	52.65 (10.41) 2.33
Shift C	−0.18 (6.84) 1.46	0.45 (7.09) 1.51	2.95 (7.19) 1.61	2.20 (7.52) 1.68

Abbreviations: A = T-PEMF treatment; B = sham treatment; C-F = colour–form; Shift C = shift cost

Table 3. Means, standard deviations, and mean standard error (MSE) for colour, form, colour–form, and shift costs for 42 adults with depression (Group A) and 42 adults with ADHD (Group B)

Group	A. Baselne	End point	B. Baseline	End point
	M (SD) MSE	M (SD) MSE	M (SD) MSE	M (SD) MSE
Colour	25.38 (5.31) 0.82	23.86 (4.71) 0.73	25.90 (6.13) 0.95	20.81 (3.83) 0.59
Form	29.52 (5.20) 0.80	27.48 (4.41) 0.68	29.93 (8.15) 1.26	23.19 (4.21) 0.65
C-f	55.81 (10.21) 1.58	52.02 (8.50) 1.31	57.69 (12.23) 1.88	45.19 (6.88) 1.06
Shift C	0.95 (7.13) 1.10	1.67 (7.17) 1.11	5.69 (8.21) 1.27	0.95 (4.67) 0.72

Abbreviations: A = depression; B = ADHD; C-F = colour–form; Shift C =shift cost

normal (ln) transformation. One-way ANOVA with *post hoc* analysis of naming times (ln) indicated statistical differences between groups for colour ($F_{3,\ 164} = 11.37$; $p < 0.0001$; $\eta^2 = 0.17$), form ($F_{3,\ 164} = 20.25$; $p < 0.0001$, $\eta^2 = 0.27$), and colour–form naming ($F_{3,\ 164} = 26.85$; $p < 0.001$; $\eta^2 = 0.33$) with effect sizes in the low to medium range. For colour naming, *post hoc* analysis indicated longer times for the ADHD group at baseline than at end point (Scheffe 4.77; $p < 0.0001$), but there was no statistical difference between the depression and the ADHD group. After treatment (end point), colour-naming times were longer for the depression than for the ADHD group (Scheffe 3.09; $p = 0.026$). For form naming, times were longer at baseline than at end point for both the depression (Scheffe 3.38; $p = 0.011$) and the ADHD groups (Scheffe 5.68; $p < 0.0001$). At end point, form-naming times were longer for the depression than for the ADHD group (Scheffe 4.07; $p = 0.001$). For colour–form combinations, naming times were also longer at baseline than at end point for the depression (Scheffe 3.33; $p = 0.013$) and the ADHD groups (Scheffe 8.11; $p < 0.0001$). At end point, the colour–form-naming times were longer for the depression group than for the ADHD group (Scheffe 3.75; $p = 0.004$). One might question whether the fact that naming times were longer before than after treatment in both clinical groups might reflect changes resulting from retesting. Normative studies of healthy adolescents and adults between ages 15 and 60 years of age indicate tests–retest correlations (Pearson *r*) of 0.91 for colour, 0.93 for form, and 0.95 for colour–form naming. With these levels of reliability, the standard errors of measurement (SEMs) are small, if not minute and the data for colour–form naming can be used as an example. With a colour–form test–retest correlation coefficient (*r*) of 0.95, and an SD of 5.78 s, the resulting SEM for colour–form naming is 1.30 s, and the 95% confidence interval covers about ±2.60 s. For the group with depression, the 95% intervals for the baseline and end point means overlap slightly, but for the ADHD group there is no overlap between the baseline and end point confidence intervals. Figure 1 shows the plots and regression lines for colour–form naming for each clinical group at baseline and at end point. Patients in both groups were ranked on the basis of the end point measures.

Shift costs (s), after establishing that normality was accepted, were compared with one-way ANOVA and indicated statistical differences between groups ($F_{3,\ 164} = 4.54$; $p = 0.004$; $\eta^2 = 0.08$), but the effect size was small. *Post hoc* analysis indicated that at baseline, shift costs were larger for the ADHD group than for the depression group (Scheffe 3.14; $p = 0.022$); and, in the ADHD group, the shift costs were larger at baseline without medication than at end point with methylphenidate (Scheffe 3.14; $p = 0.022$). There was no statistical between-group difference in shift costs at end point.

We calculated the average reduction in the colour–form-naming times (s) from baseline to end point for each clinical group. The mean time reduction was 7.17 s (SD = 8.28 s; range = −13–26 s) for adults with depression and 16.07 s (SD = 8.09 s; range = 5–46 s) for adults with ADHD. We then tested the associations (Pearson *r*) between the baseline colour–form times and the size of the gains (time reductions), after establishing that normality was accepted for both distributions. Correlation *r* was .84 ($r^2 = 0.68$; $p < 0.0001$) for the group with ADHD and .58 ($r^2 = 0.34$; $p < 0.0001$) for the group with depression, and the effect sizes were large for both groups. The difference in magnitude, expressed in Fisher *z* (*q* value), between the correlation coefficients (*r*) for the clinical groups was $q = 1.22 - 0.66 = 0.56$ and of large effect size and therefore of clinical significance. The index of forecasting efficiency (*E*) for the ADHD group was $E = 0.43$ and for the depression group $E = 0.19$, resulting in a 24% greater predictive strength in the ADHD than in the depression group (Cohen, 2009).

Discussion

This is the first study that used the AQT processing-speed and efficiency measures with a group of adults with treatment-resistant

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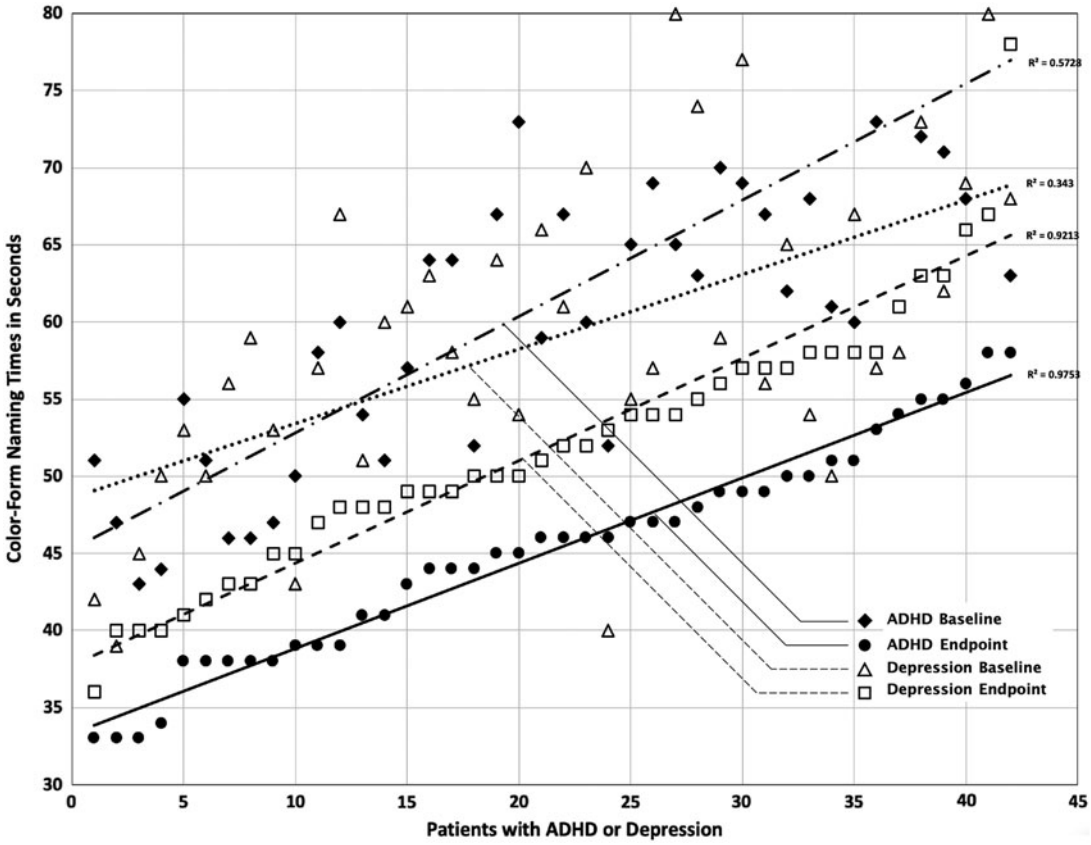

Fig. 1. The plots and regression lines for colour–form naming for each clinical group at baseline and at end point. Patients in both groups were ranked on the basis of the end point measures.

depressive disorder and that directly compared the performances with those of patients with ADHD without depression. Based on the accounts of the characteristics of the cognitive problems in depression and ADHD, we hypothesised that the AQT measures of cognitive speed (colour–form naming) and the derived shift-cost measures of processing efficiency (cognitive overhead) would differentiate the two clinical groups. The results of the present comparison of baseline and end point measures of active attention (colour–form naming) and cognitive overhead (shift costs) supported this hypothesis. Moreover, the results supported the differences in the cognitive problems associated with depression and ADHD, as previously described (Barkley & Brown, 2008; Gonda et al., 2015). The cognitive problems associated with depression have been reported as primarily associated with deficits in the reaction and response time, reflected as a general slowing (5). In contrast, the cognitive problems associated with ADHD are known to result in executive deficits that involve the central executive, which controls attention and working memory and cognitive control over shifting the cognitive focus (set-shifting) (1).

In the group with depression, the perceptual speed measure for form naming and the cognitive-speed (colour–form) measure was slower at baseline than at end point after treatment. In the group with ADHD, both perceptual (colour and form) and cognitive speed (colour–form) proved slower at baseline than at end point after treatment with maximum dose methylphenidate. It was anticipated that at baseline before treatment with methylphenidate, cognitive speed (colour–form) would be slower and shift costs larger in the group with ADHD than in the group with depression. In the group with depression, shift costs at baseline and end point were well within the average–normal range (<±5 s) for adults in the same age range and remained unchanged with treatment (Nielsen & Wiig, 2011a). In the group with ADHD without depression, shift costs were larger at baseline than at end point and were reduced to within the average–normal range after treatment with methylphenidate. This finding corresponds with the outcome of a previous comparison of shift costs in adolescent and adult psychiatric referrals with and without ADHD (Wiig & Nielsen, 2012).

From a clinical perspective, an important finding might be that in the depression group, we observed incremental increases in cognitive speed (colour–form) after each week of treatment and that a decrease of 0.74 s corresponded to a decrease of 1 point on the Hamilton 6-item subscale. The reason why AQT did not differentiate the depression groups in the T-PEMF study might be that in depression, psychomotor inhibition is one of the last symptoms to diminish. When the active and sham T-PEMF depression groups were combined, and outcomes were compared to the ADHD group, the colour–form-naming times at baseline were predictive of the amount of gains in cognitive speed (time reductions) after treatment. The associations between the cognitive speed measures at baseline and the increases in cognitive speed (time reductions) indicated that the predictive strength was 24% greater in the group with ADHD than in the group with depression. In the present group with ADHD, the previously reported response pattern for adults with ADHD with or without comorbid depression before medication with methylphenidate was repeated (Nielsen & Wiig, 2011b; Nielsen et al., 2017; Magell et al., 2018). For the patients with ADHD, the longer than average cognitive speed and larger than

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average shift-cost measures were normalised for 76% of patients in response to treatment with the maximum methylphenidate dose.

There were several clinically relevant distinguishing characteristics between the processing-speed profiles associated with depression and ADHD without depression. The most obvious is that treatment-resistant depression did not appear associated with major deficits in active attention, working memory, or set shifting (cognitive speed) or processing efficiency (shift cost), as measured by AQT. In this study, the average shift costs in the depression group were well within the average–normal range (±<5 s) both at baseline and at end point. The processing-speed response profile for the group with depression also conformed to the additive model reported for healthy adult peers of their age in which the sum of the colour- and form-naming times equalled the colour–form-naming time ±5 s (Wiig et al., 2007; Nielsen & Wiig, 2011a). Moreover, shift costs remained stable during both the T-PEMF active and sham treatments in the depression group, as shown in the overview of the weekly treatment outcomes (see Table 1). This suggests that the shift costs in depression reflect primarily the added time needed for the phonological–sequence representation of colour–form combinations and that active attention and cognitive control are not, or only minimally, affected. The finding that all processing-speed measures (colour, form, colour–form) were at the upper limits of the average–normal range at baseline and improved only slightly after treatment for adults with depression further suggests that generally observed reductions in psychomotor skills may have affected all processing-speed measures equally. In contrast, the cognitive-speed and shift-cost measures for the group with ADHD without depression group were in the larger than average ranges (>±5 s) at baseline and were reduced to well within the average–normal range with maximum doses of methylphenidate, indicating improved active attention and cognitive control. This pattern was also observed in earlier dose-monitoring studies with both medication-naive and previously medicated patients, some of whom exhibited depression as a comorbidity (Nielsen et al., 2017; Magell et al., 2018; Wiig & Nielsen, 2012). In the depression group, a second clinically relevant observation might be that there was a measurable and incremental increase in cognitive speed (colour–form) after each week of treatment and that a time reduction of 0.74 s in colour–form naming corresponded to an increase of 1 point on the Hamilton 6-item subscale. Moreover, neither naming times nor shift costs were negatively affected by the use of sedating drugs. In combination, the findings suggest that AQT may be used to monitor responsiveness to treatment of depression and possibly to identify nonresponders, the hypotheses that need further clinical investigation.

The study has several limitations to be considered in interpreting findings, among them is the fact that the diagnostic groups with depression or ADHD without depression were not matched one-on-one for age or gender. A second limitation is that no clinical group with depression and comorbid ADHD or a matching group of healthy individuals was included in the study. A third limitation is that, due to the selection of a group of patients with treatment-resistant depression for this study, we cannot extend the findings to patients with depression in general. These limitations indicate a need for further, independent validation.

From a pragmatic, clinical perspective, the findings showed that AQT was user-friendly and time efficient (about 5 min.), even for the severely depressed, treatment-resistant patients studied. We found that, in contrast to what has been observed in adults with ADHD, shift costs, a measure of processing efficiency and cognitive control, were relatively small in the sample of patients with depression and comparable to those seen in healthy adults in the same age range both at baseline and following treatment. The processing-speed measures for patients with depression were only moderately associated with depression severity, as measured by the Hamilton Depression Scale. There was, however, a predictive relationship between decreases in naming times with treatment and increases in the Hamilton 6-item subscale. The combined findings suggest that for adults with ADHD with comorbid depression, the degree of depression may influence the processing speed to a mild or moderate degree but should have minimal additive effects on executive functions assessed by the cognitive-speed and processing-efficiency measures obtained by the experimental tests used in this study. In the future studies of depressed patients it should be considered to administer AQT after remission to gain insight into any residual cognitive symptoms.

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Authors contributions. Klaus Martiny, MD, and Niels Peter Nielsen, MD, conceptualised the study design. Klaus Martiny collected the processing-speed data for adults during treatment for depression.

Niels Peter Nielsen collected the processing-speed data for adults with ADHD before and after treatment with methylphenidate.

Elisabeth H. Wiig, PhD analysed the data for the comparison of processing-speed profile in the clinical groups before and after treatment. Klaus Martiny, Niels Peter Nielsen, and Elisabeth Wiig interpreted the data and Klaus Martiny and Elisabeth Wiig collaborated on writing the manuscript. Klaus Martiny, Niels Peter Nielsen, and Elisabeth Wiig reviewed and edited manuscript drafts at various stages and accepted the final manuscript for submission.

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Authors Niels Peter Nielsen, MD, and Elisabeth H. Wiig, PhD hold the copyright to A Quick Test of Cognitive Speed with coauthor Professor Lennart Minthon. They report no other financial or personal conflicts of interest.

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