Individual Variability in Reaction Time and Prediction of Clinical Response to Methylphenidate in Adult Attention-Deficit Hyperactivity Disorder: A Prospective Open Label Study Using Conners' Continuous Performance Test II

Objective: The aim of this study was to examine whether reaction time parameters in adult patients with Attention Deficit Hyperactivity Disorder (ADHD) could predict their response to methylphenidate (MPH).

Method: Previously unmedicated patients (N=123) were administered the Conners' Continuous Performance Test II (CPT II) at baseline and after 6 weeks of treatment with immediate-release MPH. In addition to traditional CPT measures, we extracted intra-individual raw data and analyzed time series using linear and non-linear mathematical models.

Results: Clinical responders, assessed with the Clinical Global Impression-Improvement scale, showed significant normalization of target failures, reduced variability and skewness, and increased complexity of reaction time series after 6 weeks of treatment, while nonresponders showed no significant changes. Prior to treatment, responders had significantly higher variability and skewness, combined with lower complexity, compared to non-responders.

Conclusion: These results show that the CPT test is useful in the evaluation of treatment response to MPH.

Keywords: Adult ADHD Treatment, Reaction Time, Intrasubject Variability, Continuous Performance Test, Methylphenidate

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental psychiatric syndrome characterized by age-inappropriate and impaired levels of attention, impulsivity and motor overactivity according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013) (DSM-5). The condition typically manifests itself during childhood and persists into adulthood for the majority of patients (Biederman, Petty, O'Connor, Hyder, & Faraone, 2012; Kessler et al., 2005; Lara et al., 2009; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Vitola et al., 2016). ADHD is associated with adverse academic and occupational outcomes, impaired somatic and psychiatric health, as well as high costs for health care and other social services. (Biederman & Faraone, 2005; Biederman, Petty, Evans, Small, & Faraone, 2010; Fredriksen, Dahl, Martinsen, Klungsoyr, Faraone, et al., 2014; Nigg, 2013; Willcutt et al., 2012). However, a significant proportion of ADHD cases are diagnosed in adulthood, indicating some heterogeneity of the developmental trajectory of this syndrome. Symptoms of hyperactivity and impulsivity may decline during adolescence, while inattention problems tend to persist (Faraone, Biederman, & Mick, 2006).

Although it has not been possible to identify a single neurocognitive defect linked to ADHD (Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock, 2005), this heterogeneous syndrome is commonly attributed to several cognitive dysfunctions, such as impairments of working memory and inhibition, delay aversion, decision making, timing and variability (Barkley, 2010; Biederman et al., 2006; Coghill, Seth, & Matthews, 2014; Hart et al., 2014; Noreika, Falter, & Rubia, 2013; Sergeant, Geurts, Huijbregts, Scheres, & Oosterlaan, 2003). Continuous performance tests (CPTs) are widely used neuropsychological tasks to assess specific cognitive components of inattention and variability. These tests were initially applied to identify attention lapses in patients with epilepsy (Rosvold, Mirsky, Sarason, Bransome, &

Beck, 1956; Wasserstein, 2005) and were originally considered to measure at least two important neurocognitive domains associated with ADHD: Attention and response inhibition.

The tasks of the CPTs require the examinee to respond rapidly when presented with a target stimulus and to inhibit response when shown a distracter stimulus. Today, the most widely used CPT is the Conners' Continuous Performance Test, which emphasizes process analysis of change and variability as a function of time on task (Rabin et al., 2014). Multiple response dimensions are computed including omission errors, commission errors, reaction time and different types of variability (Conners, Epstein, Angold, & Klaric, 2003; Riccio, Waldrop, Reynolds, & Lowe, 2001). The main advantage of this test is the ability to differentiate between impaired sustained attention and reduced vigilance as possible mechanisms mediating attention deficit (Egeland & Kovalik-Gran, 2010). However, the high signal-to-noise design of Conners' CPT tends to automatize an active response style, resulting in a higher number of commission errors, which implies an oversensitivity to this measure of presumed impulsivity (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001).

Multiple studies have demonstrated an increased reaction time (RT) variability in persons with ADHD (Epstein et al., 2003; Kofler et al., 2013). Thus, intraindividual variability has been proposed as a candidate intermediate endophenotype of ADHD (Vaurio, Simmonds, & Mostofsky, 2009). Gender differences have also been reported, with relatively less intraindividual variability with reinforcement in boys than in girls with ADHD (Rosch, Dirlikov, & Mostofsky, 2015). In other CPT-like tasks, greater RT variability has been shown in several studies in children with ADHD (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; Castellanos et al., 2005), and some studies of hyperactive children suggest that this parameter of the CPT may even be sensitive to ADHD drug treatment (Conners, Eisenberg, & Barcai, 1967; Losier, McGrath, & Klein, 1996). Increased RT variability has also been reported in adults with ADHD, although this was not specific to ADHD (Kofler et al., 2013).

Psychostimulant medications are the most frequently prescribed drugs to alleviate the behavioral complex of inattention, impulsivity, and hyperactivity associated with ADHD. The stimulants are believed to exert their effect on the catecholaminergic systems, as they amplify the actions of dopamine and norepinephrine (del Campo, Chamberlain, Sahakian, & Robbins, 2011). The stimulant methylphenidate (MPH) is a cornerstone in pharmacological treatment of ADHD in adults (Faraone & Glatt, 2010; Fredriksen, Halmoy, Faraone, & Haavik, 2013) and the majority of the MPH treatment studies have indicated improvement on at least some aspect of CPT performance (Riccio et al., 2001). Although the responses on the CPT appear to be somewhat task and dose dependent, the majority of studies indicate that RT is decreased and less variable after stimulant medication (Losier et al., 1996).

While MPH is generally shown to be an effective treatment, the moderate efficacy found in studies also implies that a significant proportion of patients may have weak treatment response, and some experience adverse reactions (Cunill et al., 2016; Stuhec et al., 2015). Currently, there exist no reliable methods to predict how patients will respond to this medication, other than being exposed to it (Johnston, Coghill, Matthews, & Steele, 2015). However, this is not unique for ADHD, as the prediction of treatment response in psychiatric disorders is inherently difficult (McMahon, 2014). A number of studies have examined response to medication in ADHD patients, to see whether baseline measures can be used to predict treatment response, primarily using clinical variables and neuroimaging markers (Buitelaar et al., 2011; Coghill, Rhodes, & Matthews, 2007; Ishii-Takahashi et al., 2015; Johnston et al., 2015; Kim, Sharma, & Ryan, 2015). In such studies, different statistical methods and machine learning approaches have been employed (Kim et al., 2015; Wong et al., 2017).

Two studies compared reaction time variability between responders and non-responders in ADHD children treated with MPH (Lee et al., 2009; Park et al., 2013). Lee et al

(2009) examined Korean children with ADHD to determine whether pretreatment RT variability could predict response to MPH (n = 90). Non-responders showed significantly greater RT variability at baseline, and the authors concluded that a high baseline RT variability predicted poor response to MPH. In a post-hoc study from an open-label 12 week trial of MPH in Korean children with ADHD by Park et al. (2013), the baseline severity of neuropsychological deficit was also found to be predictive for response. Low baseline omission errors and low response time variability scores on the CPT were associated with a significantly higher probability of clinical response to MPH. Both studies concluded that high baseline variability is associated with poor response to MPH.

In the present study, our aim was to examine whether pretreatment CPT measures could predict response to MPH medication in adult ADHD patients, and thus be useful for therapy planning for the adult ADHD population. In addition to traditional measures obtained from the CPT II test (Conners et al., 2000) we wanted to look at the complexity of the intraindividual times series by extraction of the raw data from the CPT test, a continuous series of 360 reaction times from each patient. A previous study using the CPT II test (Fasmer et al., 2016) found that adult ADHD patients showed reduced complexity of the time series, using sample entropy and symbolic dynamics as measures of complexity compared to controls. Such methods may provide information in addition to that obtained by traditional linear methods (Hauge, Berle, Oedegaard, Holsten, & Fasmer, 2011), and can be used to predict how systems will change over time. For instance, it has been shown that in patients with heart disease, reduced complexity, measured by approximate entropy and sample entropy, can predict death from ventricular arrhythmias (Zhuang et al., 2008).

In accordance with the previously cited studies on children, our hypothesis was that pretreatment measures of inattention and variability of RT measured by the CPT II (Abikoff

et al., 2002), and supplemented with complexity measures, would be predictive for clinical response to MPH treatment in adults with ADHD.

Method

This is an investigation of data from a prospective observational study conducted at the Specialist Outpatient Clinic at Vestfold Hospital Trust. Participants were recruited to this study from patients referred from August 2009 to December 2010 (Fredriksen, Dahl, Martinsen, Klungsoyr, Haavik, et al., 2014). The study was approved by the Regional Committee of Medical Health Research Ethics (REC South-East Norway; 2009/S-07339a [2.2007.2008]), and the Norwegian Social Science Data Services (NSD; 2009/20597/2/IB), and the research was carried out in compliance with the Helsinki Declaration. All participants signed informed consent forms prior to acceptance into the study, and since the study design was purely observational, none of the participants received any form of intervention other than the currently prevailing clinical diagnostics and treatment.

Participants

Referred patients, aged 18 to 60 years, were enrolled consecutively. For inclusion, they were assessed by two board certified psychiatrists, and had to fulfill the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision (DSM-IV TR) criteria for ADHD (Association, 2000). Exclusion criteria were any major mental disorders considered to be in need of other treatment, such as psychosis, major depression with melancholia or suicidal ideation, panic attacks with increasing frequency, or current alcohol- or substance abuse with a duration of at least three months. Exclusion criteria also included any medical contraindications for stimulant treatment such as hyperthyroidism, cardiovascular diseases or cardiac arrhythmias, or having previously tried stimulant medication either in adulthood or

during the last five years for patients 18 years of age. Participants with clinical symptoms and behaviors consistent with a pervasive developmental disorder/autism spectrum disorder or IQ below 70 were also excluded.

During the inclusion period, data from a total of 170 patients were available for analysis of CPT II. For analyses, patients with only one registration on CPT II were excluded (n = 6). In addition, due to questionable validity of the individual test, patients with three or more consecutive missing responses from the first or second registration, were also excluded (n = 30). Hence, data from a total of 134 patients were analyzed, and of these, 123 were treated with methylphenidate at the six weeks visit, and thus included for the follow-up analysis. For comparison baseline characteristics of the excluded patients are shown in the Supplementary Table.

Diagnostic assessments

Other data from this observational study have been previously published (Fredriksen, Dahl, Martinsen, Klungsoyr, Faraone, et al., 2014; Fredriksen, Dahl, Martinsen, Klungsoyr, Haavik, et al., 2014). Therefore, the assessments and study protocol will only briefly be described here. Two board-certified psychiatrists assessed ADHD diagnoses based on DSM-IV Text Revision criteria by a multisource procedure (Haavik, Halmoy, Lundervold, & Fasmer, 2010), using the Norwegian version of the Diagnostic Interview for ADHD in Adults, second edition (DIVA 2.0) (Kooij & Francken, 2010). Comorbid mental disorders were examined by the structured criteria-based Norwegian version 5.0.0 of the MINI International Neuropsychiatric Interview Plus (M.I.N.I.-Plus) for DSM-IV (Leiknes, Leganger, & Malt, 2009; Sheehan et al., 2002) including evaluation for mood disorders, anxiety disorders, somatoform disorders, psychotic disorders, eating disorders, and alcohol and substance use disorders. Participants

meeting criteria for co-morbid mental disorders were still included if ADHD symptoms could not be better explained by comorbidity.

Medication procedures

All patients received immediate-release MPH hydrochloride (MPH-IR) (Novartis Pharmaceuticals UK Ltd.) with a standard titration procedure for the first six weeks. Titration of MPH medication started with a dose of 5 mg twice a day, and continued with gradual increments of 10 mg weekly and allowed frequency of administration up to three times a day, and up to a maximum daily dose of 60mg, based on the Summary of Product Characteristics. Psychosocial interventions included psychoeducational supportive counseling at scheduled visits, offered by specialized nurses who were trained to ensure the best possible uniformity.

Health care staff administered and supervised urine screenings for patients with any substance use over the last year to ascertain abstinence from narcotics. Urine samples were screened for amphetamines, benzodiazepines, cannabis and opioids on Vitros FS 5.1 (Ortho-Clinical Diagnostisc, USA) with reagents from the supplier. Adherence to medication was assessed by interviews and accounts of prescriptions. Taking the prescribed dose less than 70% of days during last period was considered non-compliant. Non-announced blood-sampling and examination of MPH plasma-concentration from 12 consecutive patients were performed in a pilot study. All patients claimed to have taken their medication 2-3 hours earlier the same day, and the plasma levels of ritalinic-acid were compatible with intake of therapeutic amounts of methylphenidate in all cases (MPH mean daily-dose 47.0 mg, *SD* = 16.5), the mean plasma-concentration was 1962 nmol/l (*SD* = 742, range 798 – 3889).

The Clinical Global Impression (CGI) scale

Response to treatment was assessed by two outcome measures; primarily the clinical improvement by the Clinical Global Impression (CGI) scale (Guy, 1976), and secondarily by the objective Clinical Confidence Index of the Conners' Continuous Performance Test II (version 5 for Windows) (CPT II) (Conners et al., 2000).

The CGI is a widely used research rating tool for psychiatric disorders, and is assessed by clinicians as an outcome measure in psychopharmacological studies providing information of individual severity of illness and overall effects of treatment (Biederman et al., 2010; Busner & Targum, 2007; Kooij et al., 2004; Rosler, Fischer, Ammer, Ose, & Retz, 2009). We applied the Clinical Global Impression-Improvement scale (CGI-I), a single-item global Likert-type 7 point scale that requires the investigator to assess the patients' degree of change from the intervention from baseline (very much improved = 1 to very much worse = 7). The CGI-I scale has been found sensitive to changes of drug treatment (Lloyd et al., 2011). In this study a responder was defined by dichotomized values of much or very much improved (CGI-I score 1 or 2).

To assess interrater reliability between the investigators on the CGI scale, during the initial phase of the study, patients (n = 22) were prospectively evaluated independently by both investigators on the corresponding seven point CGI scale of severity (CGI-S). The intraclass correlation coefficient between the two investigators was 0.78 with respect to their average measures.

Variables of the Conners' Continuous Performance Test II

Prior to analysis, the overall normative statistics by the Confidence Index (CI) supplied by the CPT II v.5.0 were chosen to assess a secondary outcome (dependent variable) of treatment

response. Several subtests of the CPT test paradigm were then applied to measure different aspects of attention and response-inhibition as independent variables (Conners et al., 2000).

In the CPT II, three hundred sixty (360) letters, presented one at a time for approximately 250 milliseconds each, are presented in the standard format of 18 sub-blocks of 20 trials each. The blocks differ in the interstimulus intervals (ISI) between letter presentations which last 1-, 2-, or 4-seconds. Interstimulus intervals are randomized between blocks so that all three ISI conditions occur every three blocks. Transition from one block to the next is unannounced and occurs without delay. The subjects are instructed to press the spacebar when any letter except the letter "X" appeared on the screen. The percentage of trials when letters other than "X" appear is 90% across all ISI blocks. Reaction time is measured from the point at which any letter other than "X" appears on the screen until the spacebar was pressed (Go trial). No-Go trials occur when an "X" is presented. Two types of errors are recorded. Errors of omission occur when the participant fails to respond to a target stimulus. Errors of commission occur when the participant responds to a non-target stimulus (i.e., "X"). The total Conners CPT task takes 14 minutes to complete.

The CPT II Confidence Index (CI) provides a confidence level produced by a discriminant function analysis of maximum likelihood estimation, and expressed as a percentage of cases out of 100 that would be correctly classified as clinical (Conners et al., 2000). Indexes above 50 are obtained when the profile more closely matches a clinical profile, while indexes less than 50 are obtained when the profile is a closer match to a non-clinical profile. In this study, we applied a dichotomized secondary outcome of response defined as reduction by 10 indexes or more of the CI, which inversely improved non-clinical match by 10 indexes or more.

From the conventional analyses of the CPT II data, the following measures are reported: Reaction time for correct responses (hit reaction time in millisecond), and variability

of the reaction time standard error, which is the standard deviation of the standard error values of the individual's reaction time varies between the 18 sub-blocks. Numbers (%) of omission and commission errors (%) were also recorded.

In addition to these measures, we also analyzed the raw data of whole series of reaction times, containing 360 data points for each participant. Missing values were replaced with the mean of the time series. We calculated the standard deviation of reaction time (SD RT) expressed as percent of the mean value, the root mean square successive difference (RMSSD), also expressed as percent of the mean value, describing the difference between successive reaction times, and skewness. Furthermore, we employed two measures of complexity, sample entropy and symbolic dynamic analysis as explained below.

Sample entropy

For the analysis of sample entropy, the data were normalized by transforming the time series to have sample mean 0 and sample variance 1. Sample entropy is a nonlinear measure, indicating the degree of regularity (complexity) of a time series, and is the negative natural logarithm of an estimate of the conditional probability that subseries of a certain length (m) that match point-wise, within a tolerance (r), also match at the next point. We chose the following values, $m = 2$ and $r = 0.2$. Sample entropy was used since it can be employed with comparatively short time series (> 50) and is robust with regard to outliers (Richman & Moorman, 2000). The software used for the estimation of sample entropy was obtained from the Physio Toolkit Research Resource for Complex Physiologic signals (Goldberger et al., 2000) (see http://www.physionet.org).

Symbolic dynamics

The time series were transformed into series of symbols based on the method described by Guzzetti et al. (2005) and Porta et al. (2007). The difference between the maximum and minimum value was divided into 6 equal portions (1 – 6) and each value of the series was assigned a number from 1 – 6, such that the transformed time series consisted of a string of numbers from 1 – 6. To avoid the problem with outliers the maximum value was set at no more than the mean + 3 times the SD, and the minimum value was set at no less than the mean – 3 times the SD. The series were then divided into overlapping sequences of three consecutive numbers. The series thus contained 358 such sequences, and the number of different sequences was counted, giving an indication of the complexity of the time series (Mujica-Parodi, Yeragani, & Malaspina, 2005).

Statistical Analysis

Student's t-test was used to evaluate differences between two independent groups, and for paired samples when comparing repeated measures of continuous variables pre-treatment and at follow-up, all tests with the p-value set at 0.05. Chi-square test and Fisher's exact test were employed for categorical variables. We did not use Bonferroni corrections since most of the measures are correlated. To display predictive properties of the independent parameters receiver operating characteristic (ROC) curves were constructed for the measures that showed significant differences between baseline and 6 weeks assessment (Zweig & Campbell, 1993). Area under the curve (AUC) was calculated, and we performed test of asymptotic significance (with null hypothesis true area = 0.5). The SPSS version 24 (IBM SPSS Statistics 24) was used for the statistical analyses. Effect size by Cohen's d was indicated when relevant, and for the paired samples t-test calculated by correction for dependence by correlation within paired variables (Morris & DeShon, 2002).

Insert Table 1 about here

Results

Baseline characteristics

A total of 123 patients were treated with MPH and completed measurements before treatment and at 6 weeks follow up. There were no statistically significant differences in the baseline characteristics between the included and excluded patients of the sample (Supplementary Table). Pretreatment we found no significant differences in sample characteristics between the responders and the non-responders using the CGI-I change at six weeks follow-up as the primary response criterion (Table 1). Recorded sample characteristics included age, gender, educational level and parents' educational level, vocational status, severity of ADHD, ADHD subtype or presentation, and psychiatric comorbidities. Seventy-seven patients (63 %) responded to treatment using the clinician assessed CGI-I response criterion (Table 1), while 54 (44 %) responded using the secondary CPT II defined outcome the Confidence Index (CI) (Table 3). Forty patients (33 %) were responders using both CGI-I and CI as a combined criterion (data not shown).

Insert Table 2 about here

Changes from baseline on stimulant treatment

For the total patient group, there were significant differences on most of the traditional CPT measures between pre-treatment and at six weeks follow-up on MPH treatment. However, there were no significant changes in reaction time (Table 2). Both reduction of errors of omissions (mean = 2.0, *SD* = 2.3 versus mean = 1.2, *SD* = 2.0, $p < .001$) and commissions

(mean = 66.0, *SD* = 19.0 versus mean = 50.3, *SD* = 23.3, $p < .001$) and variability of the standard error (mean = 12.8, *SD* = 12.0 versus mean = 8.8, *SD* = 9.5, $p < .001$) were evident after 6 weeks of treatment. The T-scores of these variables also demonstrated statistically significant changes toward normalization on treatment (Table 2).

Variability measures from the analysis of raw data, the standard deviation of reaction time (SD RT) (mean = 33.6, *SD* = 16.2 versus mean = 26.5, *SD* = 14.3, $p < .001$), the root mean square successive difference (RMSSD) (mean = 42.0, *SD* = 22.3 versus mean = 32.6, *SD* = 19.0, $p < .001$), and the skewness (mean = 3.10, *SD* = 2.55 versus mean 2.49, *SD* = 2.47, $p = .015$) also were presented with statistically significantly reduced values for the total patient group, and the complexity by sample entropy was slightly increased (mean = 1.54, *SD* = 0.31 versus mean = 1.6, *SD* = 0.28, $p = .027$) (Table 2).

Insert Table 3 about here

Pretreatment differences between the responder and non-responder group

Patients who responded to MPH treatment were compared by the chosen CPT-II parameters at baseline to those showing no relevant improvement on the predefined outcome measures (Table 3). At baseline (i.e. pretreatment), the CGI-I responders presented with significantly higher values on the CPT II measures of variability compared to the non-responders (mean = 14.4, *SD* = 13.6 versus mean = 10.3, *SD* = 8.0, $p = .038$). There were no significant differences between T-scores at baseline for responders compared to non-responders on the traditional parameters. However, significantly higher pretreatment values were found for raw score data of SD RT (mean = 36.0, *SD* = 18.3 versus mean = 29.6, *SD* = 10.9, $p = .017$), RMSSD (mean = 45.5, *SD* = 25.4 versus mean = 36.1, *SD* = 14.2, $p = .010$), and skewness (mean = 3.48, *SD* = 2.79 versus mean = 2.47, *SD* = 1.95, $p = .020$) (Table 3).

ROC analyses of pretreatment parameters showed that clinical responders based on the CGI response criterion had an AUC value for SD RT of 0.60, for RMSSD of 0.61, and for skewness 0.61, respectively. Of 42 patients with baseline RMSSD above the mean value (RMSSD > 42.0) 31 patients were true CGI responders (74% predicted responders) compared to 46 of 81 patients (57%) below the mean (p = .064, χ^2 = 3.42) (not shown in the tables).

When comparing the responder group to the non-responder group based on the outcome Confidence Index (CI), similar differences in baseline CPT II parameters were seen, apart from additional significantly higher values of pretreatment CI and the T-score values of variability, omissions and commissions, and lower values of the two complexity measures (sample entropy and symbolic dynamic) in the responder group at baseline (Table 3). Of the 42 patients who had baseline RMSSD above the mean value (RMSSD > 42.0), 26 patients (62 %) were true CI responders compared to 28 of 81 patients (35%) with RMSSD below the mean (p = .004, χ^2 = 8.39) (not shown in the tables).

Insert table 4 about here

Differences in CPT parameters by treatment within the responder and non-responder group

Both the non-responder and the responder group were analyzed separately for changes from untreated baseline to 6 week follow up on MPH treatment in the CPT parameters within their group. Table 4 shows results from the patients who did not responded to treatment. With the exception of commission errors that were reduced, all the other measures showed no significant changes from baseline to 6 weeks.

Table 5 shows the baseline and 6 week follow-up values for the responders. For both of the response criteria, the CGI-I and CI, all CPT parameters except for mean reaction time, were statistically significantly changed. The variability of the standard error, omission and

commission errors, SD RT, RMSSD and skewness were all reduced, while the complexity measures by sample entropy and symbolic dynamic were higher on treatment. Upon treatment with MPH the changes of variability, SD RT and RMSSD had large effect sizes estimated by Cohen's *d* (0.72, 0.84 and 0.78 respectively). With CI as response criterion, results were similar to the CGI-I, but with even larger effect sizes.

Insert Table 5 about here

Discussion

To the best of our knowledge, this is the first study that has examined variability and complexity of reaction time series as predictors of MPH response in adult ADHD patients. The main findings were that patients responding to MPH treatment had higher variability and skewness, combined with a tendency for lower complexity at baseline, in comparison to patients who did not respond. In contrast, traditional CPT measures, such as mean reaction time, omission and commission errors failed to predict clinical treatment response. After 6 weeks of treatment, measures of variability and skewness were significantly reduced and the complexity measures were statistically significantly increased, but only in the group showing a clinical response to MPH.

When CGI-I was used to classify responders and non-responders, a higher number of patients were classified as responders when compared with the use of CPT II derived CI. Our CGI-I based responder rate of 63% is comparable with findings from clinical studies of efficacy (Fredriksen, 2014). Results were similar for the two responder criteria applied, but the most stringent response criterion (CI) gave more significant differences between the responder and non-responder groups. On the other hand, it can be argued that since CI is based on the results of the CPT, and the measures we have used are derived from the same

test, it would be more reasonable to use the external criterion CGI. The clinical meaning of the CI has not yet been clarified, and the more recent version of CPT (Conners Continuous Performance Test Third Edition™) does not apply this parameter. The predictive power of the present measures was found to be only moderate, with AUC values ranging between 0.59 - 0.61 using CGI-I, but higher (0.60 - 0.71) with CI. Therefore, these CPT derived parameters cannot alone predict response to MPH with sufficient certainty, but we suggest that in combination with other methods and appropriate statistical modeling techniques, they may improve our ability to predict response to MPH.

The literature presents variable and partly conflicting results concerning the use of clinical data to predict response to MPH. Age, weight, gender, comorbid anxiety or oppositional defiant disorder, IQ, academic achievement, disease duration, severity of symptoms, level of maternal ADHD symptoms and prior atomoxetine use have all been shown to have some predictive effect (Buitelaar, Van Der Gaag, Swaab-barnkvhld, & Kuipkr, 1995; Buitelaar et al., 2011; Chazan et al., 2011; Fredriksen, Dahl, Martinsen, Klungsoyr, Haavik, et al., 2014; Johnston et al., 2015; Kim et al., 2015; Setyawan et al., 2015; Treuer et al., 2014; Wong et al., 2017). It has been difficult to predict treatment response to stimulants using neuropsychological tests in ADHD patient as well, and results from these studies have also been conflicting Coghill et al., 2007; Wong et al., 2017).

Both Coghill et al. (2007) and Johnston et al. (2015) found that performance on a go/no-go task predicted the effect of MPH in children, and Kim et al. (2015), also in children, found that Stroop color word test performance was a predictor for the effect of MPH. Increased variability of reaction times is found in both children and adults with ADHD (Kofler et al., 2013), and treatment with MPH has been shown to normalize this intraindividual variability (Castellanos et al., 2005). Increased behavioral variability has also been found in studies of spontaneously hypertensive rats, an animal model of ADHD (Perry,

Sagvolden, & Faraone, 2010). However, increased variability, measured by SD, is also seen in a number of other conditions and brain affecting disorders (Kaiser et al., 2008; MacDonald, Nyberg, & Bäckman, 2006), and is therefore not specific for ADHD.

RMSSD is less often used as a measure of variability, but in the present study it gave very similar results compared to SD, indicating that changes in the short term variability, from one response to the next is not substantially different from changes in the overall variability. We have however, not explored variability in different frequency spectra (Johnson et al., 2007). While variability has often been studied in the field of ADHD, complexity has not been given a similar focus (Fasmer et al., 2016). Analysis of the complexity of the present time series showed that sample entropy and symbolic dynamics gave similar results, indicating that treatment with MPH gives time series with increased complexity, meaning reduced order and predictability. In a study of adult ADHD patients (Fasmer et al., 2016), compared to clinical controls, also using the CPT II, it was found that time series from ADHD patients was characterized by reduced complexity and increased variability, supporting the idea that reduced complexity and increased variability are associated with disease states. Therefore, the present findings of reduced variability and increased complexity following treatment of ADHD patients with MPH suggest that the treatment changes the brain towards a state of more normal function.

In a study using the fixed sequence sustained attention to response task in children undergoing treatment with MPH (Johnson et al., 2008), these children had more commission and omission errors when compared to a control group, and they demonstrated greater standard deviation of RT and fast moment-to-moment variability. Administration of MPH normalized levels of commission errors and the fast moment-to-moment variability in RT, but did not affect the rate of omission errors and the standard deviation of RT. We had no normal control group for comparison in our study, however we found that treatment with MPH

reduced both omission and commission errors. It also reduced both the standard deviation of RT and the RMSSD, which is a measure of the variability from one reaction time to the next, and thus comparable to the fast moment-to-moment variability measure. Nevertheless, the study of Johnson et al. (2008) differs from ours in terms of the choice of test for measuring attention, in addition to the age groups studied.

Our present findings are also in contrast to two other studies in children. Lee et al. (2009) examined children (ages 6 - 18 years) diagnosed with ADHD and treated for 12 weeks with OROS methylphenidate. Response times were recorded using a computerized continuous performance test with both auditory and visual modalities at baseline and at the end of the study. Sixty-seven % of the subjects responded to MPH treatment, defined as a score of less than 18 on the ADHD rating scale and a score of 1 or 2 on the CGI Improvement scale. The responders showed lower RT variability at baseline, while mean reaction time, omission and commission errors did not differ from responders. Park et al. (2013) studied children (6 - 12 years) with ADHD, and also used OROS-methylphenidate. Response times were recorded using the Continuous Performance Test (omission and commission errors, response times, and response time variability). The subjective outcome measurement was the parent version of the ADHD Rating Scale-IV, and response was defined as a 50 % decrease from baseline. In contrast to our findings, these young responders showed a lower level of omission errors and lower response time variability at baseline.

Compared to our findings, these results may indicate that children with ADHD differ from adults in terms of how variability measures predict MPH response. Previous studies have shown that variability patterns may vary between different age groups. In an imaging study, Garrett et al. (2010) found that that blood oxygen level-dependent signal variability was lower in older subjects than in younger subjects, although reaction time variability on cognitive tasks was higher. When comparing children and young adults, McIntosh,

Kovacevic, & Itier (2008) found that maturation was accompanied by increased variability of EEG-signals and reduced variability of response times in a facial recognition task. It may also be relevant to consider that adult patients with ADHD in longitudinal studies have been found to have fewer neuropsychological deficits in childhood than children with ADHD, suggesting that adult ADHD represents differences in etiology (Moffitt et al., 2015).

The effect of MPH on the brain may also differ between children and adults. A number of animal studies show that methylphenidate affects a mature nervous system differently than a developing nervous system (Urban & Gao, 2015). It is difficult to compare such findings with human data. However, there is one experimental study with humans (Schrantee et al., 2016) showing that the effect of methylphenidate, used as a probe for dopamine function, is modified by age. That study involved 99 patients with ADHD, 10 - 12 years and 23 - 40 years old, treated for 4 months with MPH, and then challenged with an acute dose of MPH. This treatment increased cerebral blood flow response to MPH in children, but not in adults, demonstrating that MPH affects a developing dopaminergic system differently than a matured system. Such findings are also compatible with known age-related changes in brain dopaminergic systems (Kaasinen & Rinne, 2002). In further studies, it will therefore be important to pay closer attention to age effects.

The present results confirm the usefulness of the CPT-II in evaluation of adult patients with ADHD, not only for establishing a diagnosis (Fasmer et al., 2016), but also for treatment planning. Additional information from this test can be obtained by extracting raw data and performing analyzes using both linear and non-linear methods. These methods may also provide relevant information for the study of brain function in ADHD and the mechanism of drug actions. A recent magnetic resonance imaging study found higher default-mode network (DMN) activation variability in adult patients with ADHD and associated impaired outcome on a reward based decision-making task. In this trial, medication with MPH improved within-

network connectivity of the DMN and visual networks, but not between-network connectivity or temporal variability (Mowinckel et al., 2017). These results indicated that MPH has differentiated and limited effects on variability of brain function in ADHD.

Strengths and limitations

This is a naturalistic study from a specialized outpatient clinic. The participating patients may therefore not be representative of persons with ADHD in the general population. Nevertheless, they are representative of patients seeking treatment, and the study group is comparatively large. Most of them have comorbid psychiatric disorders in addition to ADHD, and it is therefore difficult to differentiate the effect of ADHD from these other conditions. However, when ADHD patients are seen in an adult psychiatric setting, comorbidity with other disorders is the rule. In epidemiological studies the presence of comorbidity is also high (Haavik et al., 2010). It would of course have been desirable to have a normal control group for comparison, but this was not feasible. In the CPT the time interval between the presented letters (ISI) varies randomly, and each subject therefore received a different presentation of intervals. Randomization of intervals between stimulus events has reduced variability compared to fixed intervals in a go/no-go test (Lee et al., 2015). Thus, the presentation rate may conceivably have influenced the nonlinear measurements we have made.

As this was not a placebo controlled randomized trial, we cannot exclude that confounding factors might have interfered with the clinical outcome measures, and led to an overestimation of improvement by the CGI-I measure. Thus, our predictions may not only be a true prediction of MPH effect, but may also include some ’placebo’ effects. The CI outcome is however assumed to be less affected by placebo, and showed similar patterns of prediction and with larger AUCs than the CGI-I. Despite the response rate by the CGI-I, outcome was

not unreasonably high, its proneness for confounding may have contributed to decreased accuracy of predicted MPH response.

Using the DSM-IV defined ADHD criteria in this study implies that the sample does not include patients with onset between 8 -12 years of age, and only 5 current inattentive or hyperactive impulsive symptoms. This should therefore be noted as a limitation if generalizing findings from this study to the more extensive DSM-5 defined ADHD group.

Conclusion

Adult ADHD patients responding to treatment with MPH and tested with CPT II at baseline and at 6 weeks showed reduced variability and skewness and increased complexity of reaction time series. At baseline, patients responding to treatment had higher variability and skewness, combined with lower complexity, compared to patients that did not respond. These results confirm the usefulness of the CPT II in the evaluation of ADHD patients, and show that additional information from this test can be obtained by extracting raw data and performing analyzes using both linear and non-linear methods.

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Table 1. Sample Characteristics at Baseline by Clinical Response to Medication

	All patients		Responders*		Non-responders		*p*[a]	X^2 /F [b]
All patients (%, *n*) [a]	100.0	123	62.6	77	37.4	46		
Women (% all and within responder group)	49.6	61	49.4	38	50.0	23	.944	0.005
Men (% all and within responder group)	50.4	62	50.6	39	50.0	23		
Age categories [a]								
18 – 24 years	25.2	31	28.6	22	19.6	9	.062	7.343
25 – 34 years	34.1	42	29.9	23	41.3	19		
35 – 44 years	28.5	35	33.2	26	19.6	9		
45 and above	12.2	15	7.8	6	19.6	9		
Age (*n*=123) (mean, SD)[b]	32.3	9.5	32.3	9.1	32.4	10.4	.947 [b]	1.969
Body weight (kg) [b]	77.1	15.8	77.5	14.3	76.4	18.3	.720 [b]	1.413
Body mass index (kg/m^2) [b]	25.3	4.7	25.3	4.1	25.3	5.7	.972 [b]	2.662
Years of education [b]	11.1	2.3	11.1	2.2	11.1	2.5	.985 [b]	0.872
Achieved educational level [c]								
Not fulfilled compulsory school	5.7	7	3.9	3	8.7	4	.739[c]	1.385
Lower educational level (compulsory school)	47.2	58	49.4	38	43.5	20		
High school	36.6	45	36.4	28	37.0	17		
University (3-6 year)	10.6	13	10.4	8	10.9	5		
Living and marital status [a]								
Single/living alone	39.8	49	39.0	30	34.8	19	.821	0.395
Married/cohabiting partnership	38.2	47	40.3	31	34.8	16		
Living with parents or other caregivers	22.0	27	20.8	16	23.9	11		
Parents educational level [a]								
Mothers level of education (*n*=102)								
Lower educational level	44.7	46	48.4	31	38.5	15	.281	3.735
Senior high school	39.8	41	40.6	26	38.5	15		
University	14.6	15	10.9	7	20.5	8		
Fathers level of education (*n*=100) [a]								
Lower educational level	21.0	21	22.6	14	18.4	7	.310	2.342
Senior high school	58.0	58	61.3	38	52.6	20		
University	21.0	21	16.1	10	28.9	11		
Vocational status (*n*=122) [c]								
Unemployed or work disabled	60.7	74	63.6	49	55.6	25	.667[c]	0.782
Part time work	5.7	7	5.2	4	6.7	3		
Full time work	33.6	41	31.2	24	37.8	17		
Severity of ADHD (by the CGI-S) [d, a]								
High severity (CGI-S ≥ 5)	55.3	68	59.7	46	47.8	22	.198	1.654
Lower severity (CGI-S < 5)	44.7	55	40.3	31	52.2	24		
DSM-IV subgroups of ADHD [c]								
ADHD-Inattentive	44.7	55	39.0	30	54.3	25	.295[c]	3.764
ADHD-Combined	39.0	48	45.5	35	28.3	13		
ADHD-Hyperactive	8.1	10	7.8	6	8.7	4		
ADHD-Residual/Other	8.1	10	7.8	6	8.7	4		
Psychiatric comorbidity [e, a]								
Any mood disorder (lifetime)	48.8	60	45.5	35	54.3	25	.340	0.912
Anxiety disorder	53.7	66	49.4	38	60.9	28	.215	1.537
Alcohol use disorder	12.2	15	13.0	10	10.9	5	.728	0.121
Drug use disorder	4.9	6	6.5	5	2.2	1	.282	1.158

* Responders by the Clinical Global Impression-Improvement scale (CGI-I) defined by the investigator rated values of being "much" or "very much improved" at end-point (CGI-I score of 1 or 2). Percentages of the row characteristics are within responder groups in the columns. a. Test by Pearson chi-square, 2-sided. b. Independent *t* test, 2-sided. c. Fisher's Exact Test, 2-sided. d. The Clinical Global Impression - Severity scale (CGI-S). e. Psychiatric comorbidity assessed by the Mini International Neuropsychiatric Interview for DSM-IV (MINI), last year if not otherwise specified.

Table 2. Measures Derived from the Conners' Continuous Performance Test II at Baseline and 6 Weeks on Treatment with Methylphenidate (All Patients *N* = 123)

	Baseline	**6 weeks**	***p*** [a]
	Mean (*SD*)	Mean (*SD*)	
Traditional measures			
Reaction Time (RT)	359 (61)	362 (56)	.753
Variability (of RT Standard Error)	12.8 (12.0)	8.8 (9.5)	< .001
Omissions (%)	2.0 (2.3)	1.2 (2.0)	< .001
Commissions (%)	66.0 (19.0)	50.3 (23.3)	< .001
T-Score Reaction Time	43.6 (10.5)	44.1 (10.1)	.670
T-Score Variability	58.1 (13.7)	50.3 (12.9)	< .001
T-Score Omissions	62.4 (21.9)	54.8 (18.7)	.004
T-Score Commissions	67.2 (11.2)	59.0 (13.2)	< .001
Analyses of raw data			
SD RT [b] (% of mean)	33.6 (16.2)	26.5 (14.3)	< .001
RMSSD [c] (% of mean)	42.0 (22.3)	32.6 (19.0)	< .001
Sample entropy	1.54 (0.31)	1.60 (0.28)	.027
Symbolic dynamic	75.4 (16.5)	77.7 (16.5)	.268
Skewness	3.10 (2.55)	2.49 (2.47)	.015

The Measures are derived from the Conners' Continuous Performance Test II, Version 5 for Windows (CPT II V.5), 2004 Multi-Health Systems Inc. a. Week 6 scores on medication were compared to baseline (pretreatment) by paired sample t-test analyses, 2-sided. b. Standard Deviation of Reaction Time. c. The root mean square successive difference (RMSSD)

Table 3. Baseline Measures from the Conners' Continuous Performance Test II by Response on Treatment with Methylphenidate Compared to Non-response

	Response by the Clinical Global Impression (CGI-I) Scale [a]				**Response by the Confidence Index (CI) [b]**			
	Improvement *n* = 77	**No improvement *n* = 46**	***p* [c]**	**AUC ROC [d]**	**Improvement *n* = 54**	**No improvement *n* = 69**	***p* [c]**	**AUC ROC [d]**
Traditional measures	Mean (*SD)*	Mean (*SD)*			Mean (*SD)*	Mean (*SD)*		
Reaction Time (RT)(ms)	358 (65)	362 (52)	.709	0.56	357 (75)	361 (46)	.694	0.60
Variability	14.4 (13.6)	10.3 (8.0)	.038	0.59	15.7 (11.0)	10.6 (12.3)	.017	0.71 ***
Omissions (%)	2.2 (2.5)	1.7 (1.9)	.288	0.54	2.4 (2.2)	1.7 (2.3)	.073	0.67 **
Commissions (%)	66.8 (19.0)	64.7 (19.2)	.550	0.55	69.3 (19.8)	63.5 (18.2)	.091	0.60
Confidence Index	62.1 (23.3)	55.1 (22.4)	.106	0.57	70.0 (20.7)	51.2 (21.7)	< .001	0.74 **
T-Score Reaction Time	43.0 (11.3)	44.5 (9.2)	.437	0.57	42.3 (12.7)	44.5 (8.4)	.239	0.61 *
T-Score Variability	59.8 (14.3)	55.3 (12.2)	.080	0.58	63.4 (13.4)	54.0 (12.6)	< .001	0.71 ***
T-Score Omissions	64.2 (23.7)	59.4 (18.2)	.238	0.55	67.3 (20.5)	58.6 (22.3)	.028	0.69 ***
T-Score Commissions	67.8 (11.6)	66.2 (10.5)	.437	0.56	69.6 (12.0)	65.3 (10.2)	.033	0.64 **
Analyses of raw data								
SD RT (% of mean) [e]	36.0 (18.3)	29.6 (10.9)	.017	0.60	38.8 (16.8)	29.6 (14.6)	.002	0.71 ***
RMSSD (% of mean) [f]	45.5 (25.4)	36.1 (14.2)	.010	0.61 *	49.0 (23.9)	36.5 (19.4)	.002	0.70 ***
Sample entropy	1.50 (0.33)	1.60 (0.27)	.070	0.59	1.41 (0.32)	1.64 (0.27)	< .001	0.71 ***
Symbolic dynamic	73.5 (16.6)	78.6 (16.1)	.098	0.59	70.0 (15.6)	79.6 (16.1)	.001	0.65 **
Skewness	3.48 (2.79)	2.47 (1.95)	.020	0.61 *	3.84 (3.11)	2.53 (1.83)	.007	0.60

Treatment response is measured after 6 weeks on methylphenidate. Baseline data are measured before starting treatment on previously unmedicated patients. a. Response/ improvement by the Clinical Global Impression-Improvement (CGI-I) scale was defined by the investigator rated values of "much" or "very much improved" (CGI-I score of 1 or 2). b. Response / improvement by the Confidence Index (CI) was defined as a dichotomized outcome of a reduction by 10 indexes or more of the CI derived from the Conners' Continuous Performance Test II, Version 5 for Windows (CPT II V.5), 2004 Multi-Health Systems Inc. c. P-value of the independent samples *t*-test. d. Area under the curve (AUC) of the receiver operating characteristic (ROC), test of asymptotic significance, null hypothesis true area = 0.5, * $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$. e. The standard deviation of reaction time (SD RT). f. The root mean square successive difference (RMSSD)

Table 4. Measures Derived from the Conners' Continuous Performance Test II at Baseline and at 6 Weeks for Non-Responders on Treatment with Methylphenidate

	No improvement by the Clinical Global Impression (CGI-I) scale [a]			**No improvement by the Confidence Index (CI) [b]**		
	Baseline	**6 weeks**	***p*** **[c]**	**Baseline**	**6 weeks**	***p*** **[c]**
	***n* = 46**	***n* = 46**		***n* = 69**	***n* = 69**	
Traditional measures	Mean *(SD)*	Mean *(SD)*		Mean *(SD)*	Mean *(SD)*	
Reaction time (ms)	362 (52)	361 (44)	.924	361 (46)	366 (55)	.555
Variability	10.3 (8.0)	10.6 (12.5)	.890	10.6 (12.3)	10.1 (11.5)	.811
Omissions (%)	1.7 (1.9)	1.2 (1.5)	.167	1.7 (2.3)	1.5 (2.2)	.643
Commissions (%)	64.7 (19.2)	51.4 (23.2)	< .001	63.5 (18.2)	51.6 (24.5)	< .001
Analyses of raw data						
SD RT [d] (% of mean)	29.6 (10.9)	29.4 (18.0)	.946	29.6 (14.6)	28.7 (17.5)	.755
RMSSD [e] (% of mean)	36.1 (14.2)	36.2 (23.2)	.979	36.5 (19.4)	35.4 (23.0)	.761
Sample entropy	1.60 (0.27)	1.55 (0.32)	.436	1.64 (0.27)	1.57 (0.30)	.192
Symbolic dynamic	78.6 (16.1)	74.6 (14.2)	.212	79.6 (16.1)	77.4 (16.1)	.416
Skewness	2.47 (1.95)	2.67 (2.24)	.648	2.53 (1.83)	2.48 (2.14)	.898

Treatment response is measured after 6 weeks on methylphenidate. Baseline data are measured before starting treatment on previously not medicated patients. a. Response by the Clinical Global Impression-Improvement (CGI-I) scale was defined by the investigator rated values of "much" or "very much improved" (CGI-I score of 1 or 2). b. Response by the Confidence Index (CI) was defined as a dichotomized outcome of a reduction by 10 indexes or more of the CI on the Conners' Continuous Performance Test II, Version 5 for Windows (CPT II V.5), 2004 Multi-Health Systems Inc. c. *p*-value of the paired samples *t*-test. d. The standard deviation of reaction time (SD RT). e. The root mean square successive difference (RMSSD).

Table 5. Measures Derived from the Conners' Continuous Performance Test II at Baseline and at 6 Weeks for Responders on Treatment with Methylphenidate

	Response by the Clinical Global Impression (CGI-I) scale [a]				**Response by the Confidence Index (CI) [b]**			
	Baseline	**6 Week**		**Cohen's *d* [c]**	**Baseline**	**6 Week**		**Cohen's *d* [c]**
	***n* = 77**	***n* = 77**	***p* [d]**		***n* = 54**	***n* = 54**	***p* [d]**	
Traditional measures	Mean *(SD)*	Mean *(SD)*			Mean *(SD)*	Mean *(SD)*		
Reaction time (ms)	358 (65)	362 (63)	.677	0.062	357 (75)	356 (58)	.927	0.015
Variability	14.4 (13.6)	7.8 (7.1)	< .001	0.722	15.7 (11.0)	7.2 (5.9)	< .001	0.908
Omissions (%)	2.2 (2.5)	1.3 (2.2)	.001	0.410	2.4 (2.2)	1.0 (1.5)	< .001	0.634
Commissions (%)	66.8 (19.0)	64.7 (19.2)	< .001	0.134	69.3 (19.8)	48.5 (21.8)	< .001	1.311
Analyses of raw data								
SD RT [e] (% of mean)	36.0 (18.3)	24.7 (11.4)	< .001	0.836	38.8 (16.8)	23.5 (8.1)	< .001	1.229
RMSSD [f] (% of mean)	45.5 (25.4)	30.5 (15.7)	< .001	0.783	49.0 (23.9)	29.1 (11.3)	< .001	1.149
Sample entropy	1.50 (0.33)	1.63 (0.26)	.001	-0.397	1.41 (0.32)	1.64 (0.26)	< .001	-0.692
Symbolic dynamic	73.5 (16.6)	79.6 (17.5)	.005	-0.329	70.0 (15.6)	78.1 (17.1)	.001	-0.469
Skewness	3.48 (2.79)	2.38 (2.61)	.002	0.375	3.84 (3.11)	2.50 (2.86)	.004	0.404

a. Response by the Clinical Global Impression-Improvement scale (CGI-I) were defined by the investigator rated values of being "much" or "very much improved" at the 6 week end-point compared with baseline (CGI-I score of 1 or 2). b. Response by the Confidence Index (CI) were defined by the dichotomized outcome of a reduction by 10 indexes or more of the CI on the Conners' Continuous Performance Test II, Version 5 for Windows (CCPT II V.5), 2004 Multi-Health Systems Inc. c. Effect sizes are by Cohen's d with correction for correlation within pairs of variables. d. *p*-value of the paired samples *t*-test, 2-sided. e. The standard deviation of reaction time (SD RT). f. The root mean square successive difference (RMSSD)

Supplementary Table. Sample Characteristics at Baseline by Inclusion and Exclusion						
	Included ***n*** **= 123**		**Excluded*** ***n*** **= 47**		***p*** [a]	***X²*** **/** ***F*** [b]
Sex (%, *n*) [a]						
Women (% within column)	49.6	61	55.3	26	.504	0.446
Men (% within column)	50.4	62	44.7	21		
Age (*n*=170) (mean, SD)[b]	32.3	9.5	33.0	11.1	.682 [b]	2.394
Body weight (kg) [b]	77.1	15.8	78.1	20.3	.753 [b]	3.857
Body mass index (kg/m²) [b]	25.3	4.7	26.0	5.8	.501 [b]	3.971
Years of education [b]	11.1	2.3	10.1	1.6	.074 [b]	5.163
Achieved educational level [c]						
Not fulfilled compulsory school	5.7	7	6.4	3	.360[c]	3.211
Lower educational level (compulsory school)	47.2	58	51.1	24		
High school	36.6	45	40.4	19		
University (3-6 year)	10.6	13	2.1	1		
Living and marital status [a]						
Single/living alone	39.8	49	39.0	14	.302	2.398
Married/cohabiting partnership	38.2	47	40.3	24		
Living with parents or other caregivers	22.0	27	20.8	9		
Parents educational level [a]						
Mothers level of education (*n*=140)						
Lower educational level	44.7	46	44.7	17	.941	0.398
Senior high school	39.8	41	39.5	15		
University	14.6	15	15.8	6		
Fathers level of education (*n*=133) [a]						
Lower educational level	21.0	21	20.6	7	.372	3.133
Senior high school	58.0	58	52.9	18		
University	21.0	21	23.5	8		
Vocational status (*n*=169) [c]						
Unemployed or work disabled	60.7	74	63.8	30	.894[c]	0.225
Part time work	5.7	7	4.3	2		
Full time work	33.6	41	31.9	15		
Severity of ADHD (by the CGI-S) [d, a]						
High severity (CGI-S ≥ 5)	55.3	68	48.9	23	.458	0.551
Lower severity (CGI-S < 5)	44.7	55	51.1	24		
DSM-IV subgroups of ADHD [c]						
ADHD-Inattentive	44.7	55	25.5	12	.104[c]	6.169
ADHD-Combined	39.0	48	57.4	27		
ADHD-Hyperactive	8.1	10	6.4	3		
ADHD-Residual/Other	8.1	10	10.6	5		
Psychiatric comorbidity [e, a]						
Any mood disorder (lifetime)	48.8	60	59.6	28	.208	1.587
Anxiety disorder	53.7	66	46.8	22	.424	0.639
Alcohol use disorder	12.2	15	10.6	5	.778	0.079
Drug use disorder	4.9	6	12.8	6	.073	3.225

* *N* = 170 patients were assessed for eligibility, however data from patients with only one registration on the Conners' continuous performance test II, Version 5 for Windows (CCPT II V.5), 2004 Multi-Health Systems Inc., were useless for analyses of treatment changes, and excluded (*n* = 6) from the study. Due to validity requirements patients with three or more consecutive missing responses from any CCPT II registrations were also excluded (*n* = 30). Further, those not medicated during the six weeks treatment period (*n* = 11) were excluded, leaving *n* = 123 participants for the study. a. Test by Pearson chi-square, 2-sided. b. Independent *t* test, 2-sided. c. Fisher's Exact Test, 2-sided. d. The Clinical Global Impression - Severity scale (CGI-S). e. Psychiatric comorbidity assessed by the Mini International Neuropsychiatric Interview for DSM-IV (MINI), last year if not otherwise specified.