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Early identification of stimulant treatment responders, partial responders and non-responders using objective measures in children and adolescents with hyperkinetic disorder

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Background: The aim of this study was to evaluate stimulant medication response following a single dose of methylphenidate (MPH) in children and young people with hyperkinetic disorder using infrared motion analysis combined with a continuous performance task (QbTest system) as objective measures. The hypothesis was put forward that a moderate testdose of stimulant medication could determine a robust treatment response, partial response and non-response in relation to activity, attention and impulse control measures. **Methods:** The study included 44 children and young people between the ages of 7–18 years with a diagnosis of hyperkinetic disorder (F90 & F90.1). A single dose-protocol incorporated the time course effects of both immediate release MPH and extended-release MPH (Concerta XL, Equasym XL) to determine comparable peak efficacy periods post intake. **Results:** A robust treatment response with objective measures reverting to the population mean was found in 37 participants (84%). Three participants (7%) demonstrated a partial response to MPH and four participants (9%) were determined as non-responders due to deteriorating activity measures together with no improvements in attention and impulse control measures. **Conclusion:** Objective measures provide early into prescribing the opportunity to measure treatment response and monitor adverse reactions to stimulant medication. Most treatment responders demonstrated an effective response to MPH on a moderate testdose facilitating a swift and more optimal titration process.

Key Practitioner Message:

- Objective measures are effective in the early identification of treatment response to stimulant medication.
- Treatment response measures are available for children and adolescents from 6–18 years.
- Single dose testing with objective measures facilitates swift and optimal titration at minimal exposure to medication.
- A moderate test dose resulted in a robust treatment response in the majority (84%) of participants.
- Both, short acting as well as extended-release stimulant medications can be used to measure treatment response with objective measures.

Keywords: ADHD; Hyperkinetic disorders; Methylphenidate; Computerised testing; Drug effects

Introduction

This study used as its objective measurements a QbTest system which consists of an infrared motion camera combined with a continuous performance test (CPT).

CPT provides neuropsychological testing measuring a person's sustained and selective attention and to a lesser degree impulsivity. CPT's are generally characterised by a rapid presentation of continuously changing stimuli among which there is a designated 'target' stimulus or target pattern. The duration of the task varies but the task is intended to be of sufficient length to measure sustained attention. The CPT is reported to be the most popular clinic based measure of sustained attention and vigilance and it has been described as the most sensitive measure for monitoring medication effects (Riccio, et al., 2001).

The assessment of motoric activity during CPT is undertaken by analysing the complexity of the child's head movement pattern. Infrared motion analysis is an effective means of quantifying hyperactivity and was found to correlate significantly with commonly used teacher rating scales for children with ADHD (Teicher et al., 1996).

The work of Teicher et al. (2003, 2008) demonstrated that objective measures of primarily activity and secondarily attention performance show patterns of response to different doses of methylphenidate (MPH) and placebo that are in good agreement with blind placebo-controlled parental ratings of efficacy thus providing preliminary evidence that this office-based

assessment of the therapeutic response to stimulants has ecological validity, which is defined as the degree to which the results of a laboratory measure represents the actual behaviours of interest as they occur in natural settings (Barkley, 1991).

Teicher et al. (2003) also found that both moderate and high doses of MPH produced rate-dependant alterations in activity. Consistent with the other neuropsychological studies, MPH exerted a stronger effect on the hyperactive-distracted state than on the hyperactive-impulsive state. Similarly Hale et al. (2005), concentrating on the level of neuropsychological impairment amongst children with ADHD, found that those who showed dramatic medication effects were more likely to be diagnosed with the combined type ADHD and children who required higher dose response levels presented with more externalising and hyperactive/impulsive behaviours.

The hypothesis put forward in this study was that initiating treatment with a moderate test dose of stimulant medication allows for the early identification of treatment response (robust, partial and adverse treatment response) using objective measures of activity, attention and impulse control in children and young people diagnosed with hyperkinetic disorder who were referred to a generic child and adolescent mental health service (CAMHS) clinic.

This study represents a clinical audit on ongoing clinical work.

Method

Sample description

Our sample consisted of 44 children and young people between the ages of 7–18 years with a diagnosis of hyperkinetic disorder. The diagnosis was obtained by using the ICD-10 classification of mental and behavioural disorders and a full assessment process including a clinical interview and behavioural observation by experienced child and adolescent psychiatrists at our clinic, a medical examination and the administration of rating scales completed by parents and teachers. The Strengths and Difficulties Questionnaire (SDQ) (Goodman et al., 2000) was used as a broad band instrument to evaluate general behaviour and psychosocial functioning (see Table 1). As narrow band scales specific to ADHD symptomatology, the Conners'–Revised Rating Scale (short and long version) as well as the Conners' Abbreviated Teacher Rating Scale (Conners, 1999) were administered. Direct observation in educational settings was undertaken by the clinicians when required and reports of developmental and literacy skills tests were provided when indicated.

Twenty-four participants met criteria for hyperkinetic disorder (*F*.90.0) and 20 for hyperkinetic conduct disorder (F90.1). In addition, six participants met criteria for a specific developmental disorder of scholastic skills (F81), four met criteria for Asperger's syndrome (F84.5), three participants displayed mixed disorders of conduct and emotions (F92), three cases presented with learning difficulties (with IQ's between 70-80) and there was each one case of a phobic anxiety disorder (F93.1) and a specific developmental disorder of motor function (F82).

Inclusion/Exclusion criteria

Newly diagnosed drug-naïve participants who, according to NICE guidelines, met criteria for treatment with stimulant medication were included as well as participants who were taking medication or had been taking MPH medication in the past and were on moderate doses of MPH (see Table1).

Children and young people who were on a combination of stimulant and non-stimulant medication for hyperkinetic disorder, or who were on stimulant medication other than MPH, were excluded from this study.

Other exclusion criteria included: presence of a severe mental illness, such as early onset psychosis and mental retardation (F70-73) with an IQ <70.

Study design

A computer-administered visual go/no go vigilance response task (CPT 'X'-type) combined with motion capture was used for the younger age group of 6–12 years (QbTest). The older age group (QbTest-Plus) received a visual 'no-priming identical pairs' test (CPT:IP), increasing the degree of difficulty of the CPT to an age appropriate level (for further information and a visual description of the system go to http://www.qbtech.se/products/qbanalysis).

Motion capture was recorded by reading the coordinates of a headband marker. The position of the marker is sampled 50 times per second, and the spatial resolution is 1/27 mm per camera unit. (QbTest & QbTest-Plus Technical Manual v. 1.2, 2006).

The four parameters generated for activity measures included time active (reflects the ability to sit still), distance (amount of total activity), area (vividness of movement) and microevents (position changes >1 mm). Attention measures contained four parameters comprising of omission error (no response to target representing inattention and an inability to remain focused on the task), reaction time (the average elapsed time from stimulus presentation to button press reflecting speed of processing and execution), reaction time variation (moment to moment fluctuation in reaction time performance associated with difficulty sustaining attention, forgetfulness, disorganization and careless errors) and normalised reaction time variation (reaction time variation corrected for slow mean reaction time which often leads to high reaction time variability as a 'side-effect').

Impulse control parameters included two measures. The commission error occurs when the handheld button is pressed when the stimulus was a Non-Target and the button should not have been pressed. The commission error represents impulsive behaviour including poor response inhibition. The other parameter, anticipatory, occurs when a response is detected beyond the capability of

Table 1. Demographic and descriptive characteristics of the study sample

	Age, mean (SD)	Male (%)	Female (%)	SDQ-HYP-P, mean (SD)	SDQ-OS-P, mean (SD)	DRUG-NAÏVE (%)
QbTest (6–12 y) *n* = 24	10.2 (1.6)	19 (79)	5 (21)	9 (1.4)	23 (6.3)	20 (83)
QbTest-Plus (13-18 y) *n* = 20	15.8 (1.65)	17 (85)	3 (15)	8.9 (1.4)	22 (5.7)	3 (15)

SDQ-HYP-P indicates Strengths and Difficulties Questionnaire hyperactivity scores as completed by parents (scores of 7–10 are abnormal)
SDQ-OS-P, Strengths and Difficulties Questionnaire overall scores as completed by parents (reflects level of complexity of behavioural difficulties; scores above 17 are abnormal)

neuromuscular transmission and thus representing 'guesses'. Anticipatories are considered to originate from impulsive responding, but can also be caused by poor rule-governing behaviour.

The parameter error rate (number of incorrect button presses and non-presses divided by the number of stimuli) served as a measure of overall accuracy.

Each scoring profile was analysed to exclude the possibility of the participant misunderstanding the task. A QbTest Behaviour Rating Scale was completed by the test examiner during each test.

Retesting on medication occurred within 40 days from the baseline test since the data for QbTest demonstrates good test-retest reliability (coefficient of 0.88 for activity, 0.87 for inattention and 0.78 for impulsivity) over this time in children with ADHD (Konrad et al., 2004).

A single dose-protocol incorporated the time course effects, bioavailability and clinical efficacy of both short-acting MPH and extended-release(ER) MPH (Concerta XL, Equasym XL) (Swanson et al., 2004; Pelham et al., 2001; Gonzales et al., 2002) to determine comparable peak efficacy periods post intake.

According to the weight of the client, a moderate test dose of 0.3 mg/kg body weight was calculated and an equivalent tablet dose (5/10 mg tablets) prescribed, resulting in a mean test dose for the client group of 0.33 mg/kg body weight (n = 34; range: 0.25–0.45 mg/kg body weight).

In order to represent typical clinical practice for medication reviews, we included drug naïve and drug non-naïve clients into the study. Drug non-naïve clients were seen for a review of the treatment efficacy of their medication. Some of these cases had been established on extended-release (ER) formulations of MPH. Bearing in mind that ER medications begin by submitting an immediate release bolus that is comparable to the release of one dose of short acting medication we calculated the dose of this bolus for Concerta XL (22% of the total daily dose in immediate release form) and Equasym XL (28% of the total daily dose in immediate release form) and included clients into our study if the immediate release dose was comparable to a moderate single dose of 0.3 mg/kg/body weight. In these cases tests were performed 1.5–2 hours post intake. Other clients, especially adolescents who found it difficult to attend clinical appointments in the morning were tested on their ER preparation when according to the drug's concentration profile levels were peaking approximately 5–6 hours post intake. Only clients who were on moderate total daily doses of ER medications, i.e. 1.25 mg/kg/body weight (n = 10) were included this way. We acknowledge that expanding the range of test conditions provides a review of more practice oriented circumstances at the cost of allowing for more research standardization.

Participants who were not drug naïve and on regular MPH treatment performed the baseline QbTest after 24 hours off medication.

Informed consent was obtained prior to undertaking objective measurements with QbTest/QbTest-Plus and treatment from the parents of participating children as well as the young person and their parents.

Statistical analysis

Repeated measures analyses of variance or multivariate analyses of variance were used to evaluate treatment effectiveness with SPSS. Correlations between motion parameters and CPT measures were calculated using Pearson's Product Moment correlation.

Results

Statistically significant effects were present for all activity and attention parameters as well as for the impulse control parameter commission error (all p's < .05; see Table 2). Children and adolescents receiving medication had lower activity measures and reduced errors of omission and commission. The reaction times were shorter with reduced reaction time variation and normalised variation.

Multivariate analysis demonstrated a highly significant difference between baseline and post-MPH tests for both the QbTest group ($F = 45$, $p < 0.001$) and the QbTest-Plus group ($F = 23$, $p < 0.001$). A two way analysis of variance did not illustrate a significant difference in response to MPH between the QbTest and QbTest-Plus group ($F(1,39) = 0.57$, $p = 0.46$). Equally no differences were found between drug naïve and non-naïve responders ($F(7,35) = 1.67$, $p = .25$).

The mean scores for the anticipatory parameter were lower post medication for both children and adolescents, however the difference was not statistically significant. In the Qbtest group (ages 7–12 y) the scores did not reach statistical significance as a result of a partial response to medication in three cases (7%). These participants showed reduced activity measures but persisted with a high level of response to both targets and non-targets suggestive of a random or impulsive response profile on CPT (Teicher et al. 2004). As they were less hyperactive following the testdose their degree

Table 2. Objective measures of activity, attention and impulse control at baseline and after repetition of the test on a moderate test dose of methylphenidate (MPH) in both children (Qbtest) and adolescents (QbTest-Plus)

	QbTest (6–12 y)				QbTest-Plus (13–18 y)			
Measures	Baseline (SD)	MPH (SD)	*t*-value	*p*	Baseline (SD)	MPH (SD)	*t*-value	*p*
Time Active (%)	71.7 (19.3)	40.8 (27.5)	6.2	<.001	43.5 (23.2)	23.2 (25.7)	3.3	.004
Distance (m)	42 (20.1)	24.1 (48.8)	2.1	.048	22.9 (16.4)	11.4 (14.4)	2.5	.024
Area (cm^2)	144.8 (54)	66 (61.9)	6.1	<.001	90 (56.7)	38.3 (37.6)	3.7	.001
Microevents	18258.3 (5510.5)	9962.5 (7692.7)	5.5	<.001	10875 (5641.7)	6330 (7062)	2.5	.024
Reaction time (ms)	532.3 (103.7)	462.7 (98)	4.1	<.001	551.5 (116.4)	489.8 (151.2)	2.5	.022
Reaction time variation (ms)	314.2 (113.9)	209.8 (112.5)	4.5	<.001	214.1 (62.5)	159.4 (62.7)	3.3	.003
Normalised variation (%)	58.2 (16.8)	44.3 (20)	4.3	<.001	39.3 (10.6)	32.55 (7.7)	2.9	.008
Omission error (%)	21.2 (17.7)	9.6 (14.9)	5.4	<.001	23.5 (23)	6.6 (13.3)	2.9	.009
Commission error (%)	31.4 (16.3)	19.8 (17.2)	5	<.001	5.7 (6.4)	3 (5.2)	2.3	.032
Anticipatory (%)	10.8 (14)	7 (13)	1.2	0.252	1.8 (4.6)	1.4 (4.2)	0.4	0.688
Error rate (%)	37.1 (20.5)	21.8 (22.7)	4.2	<.001	10.6 (9.2)	4.2 (5.6)	3	.007

of disengagement or impulsivity is likely to have been measured for a prolonged period of time during CPT with increases in their anticipatory scores in contrast to children who were robust treatment responders. Anticipatory errors in the older QbTest-Plus group (ages 13–18 y) were generally infrequent (see table2) thus causing the data to be too weak to reach statistical significance.

The unusually raised but still statistically significant *p*-value for distance in the QbTest group (see Table 2) was related to one participant presenting with the highest distance measure at baseline (89 m) and whose activity measures post medication paradoxically rose to an unusually high score of 250 m, a six fold of the mean group baseline score. Equally the distance p-value in the QbTest-Plus group was affected by two out of the twenty participants showing an overall increase in their activity measures.

In comparison with the normative data, all activity scores on MPH demonstrated a return to the population mean (SD <1). This effect was less pronounced in the QbTest-Plus group. The difference between the two groups is most likely associated with age developmental alterations in the density distribution of the degree of activity. Furthermore the number of non-drug naïve patients in the QbTest-Plus group (85%) was noticeably higher compared to the QbTest Group (17%) suggesting a possible association to long-term MPH exposure. However, as described above, no significant difference in response to MPH between the QbTest and QbTest-Plus group was found.

Attention and impulse control measures on MPH also reverted to the population mean with the exception of reaction time variation and normalised variation measures in the QbTest group, once again as a result of a partial or non-response to MPH in some of the participants.

Table 3 shows the correlation analysis of association between activity, attention and impulse control measures. There was a large and significant correlation between the four activity measures: time active, distance, area and microevents ($r = 0.83–0.96$, $n = 44$, $p < .001$).

The correlation between activity and attention measures was significant with a large correlation between activity measures and omission error ($r = 0.53–0.57$, $n = 44$, $p < .001$) and a moderate correlation between activity measures and normalised variation ($r = 0.34$-0.49, $n = 44$, $p = .03$-$.001$). There was a moderate and significant correlation between activity measures and commission error ($r = 0.36$-0.47, $n = 44$, $p = .01$-$.001$).

No correlation was observed between the attention parameters omission error and normalised variation ($r = 0.15$, $n = 44$, $p = .3$). A significant correlation was reached between omission and commission error ($r = 0.51$, $n = 44$, $p < .001$).

A total of four participants (9%) had increased distance measures following MPH as illustrated in the scatter plot in figure 1. One participant's scores could not be captured in the plot because his measures were too high and outside the graph. The same participant presented with abnormal attention and impulse control measures. Another participant with increased activity measures post MPH was drug non-naïve and his baseline scores for activity, attention and impulse control unexpectedly showed to be within the normal range. In addition to the increased activity scores his attention measures also deteriorated on MPH. Of the remaining two cases who demonstrated an increase in their activity scores post MPH, one presented with a moderately hyperactive/impulsive profile and the other participant with an inattentive type profile.

Table 3. Comparison of correlation coefficients between activity measures as well as correlations between activity, attention (omission error, normalised variation) and impulsivity (commission error) measures

Measure	*p* (2-tailed)	Pearson Correlation
Distance/Time active	<.001	0.83
Distance/Area	<.001	0.95
Distance/Microevents	<.001	0.96
Time Active/Area	<.001	0.82
Time Active/Microevents	<.001	0.92
Microevents/Area	<.001	0.93
Omission/Time Active	<.001	0.53
Omission/Distance	<.001	0.57
Omission/Area	<.001	0.54
Omission/Microevents	<.001	0.57
Norm. Var./Time Active	.03	0.34
Norm. Var./Distance	.007	0.4
Norm. Var./Area	.001	0.49
Norm. Var./Microevents	.006	0.4
Commission/Time active	.01	0.36
Commission/Distance	.003	0.44
Commission/Area	.001	0.47
Commission/Microevents	.002	0.46
Omission /Norm.Var.	.33	0.15
Omission /Commission	<.001	0.51
Norm.Var./Commission	.16	0.21

Discussion

In this study measuring the effects of a single moderate testdose of MPH using infrared motion analysis combined with CPT demonstrated statistically significant medication changes. These results fall in line with other studies measuring treatment response to MPH with the help of infrared motion analysis and CPT (Teicher et al. 2003, Heiser et al. 2004, Tabori-Kraft et al. 2007). Of note is the consistency of the medication effect when adjusting the CPT task to the developmental age of the participant. Hence no difference was found in the response to the medication between the younger age group (7–12 years) undertaking a CPT X-type and the older age group (13–18 years) switching to a CPT:IP-type. As a result infrared motion analysis can be used with CPT for a broader age range adequately covering the age range of child and adolescent mental health services.

Since this study included patients established on MPH medication as well as drug naïve patients, the lack of difference in treatment response to the same dose of MPH between naïve and non-naïve participants illustrates the possible absence of a noticeable tolerance effect bearing in mind that both sides presented with comparable baseline scores. Similarly, Martins et al. (2004) reported no changes in the efficacy of MPH between children on weekend drug holidays during MPH

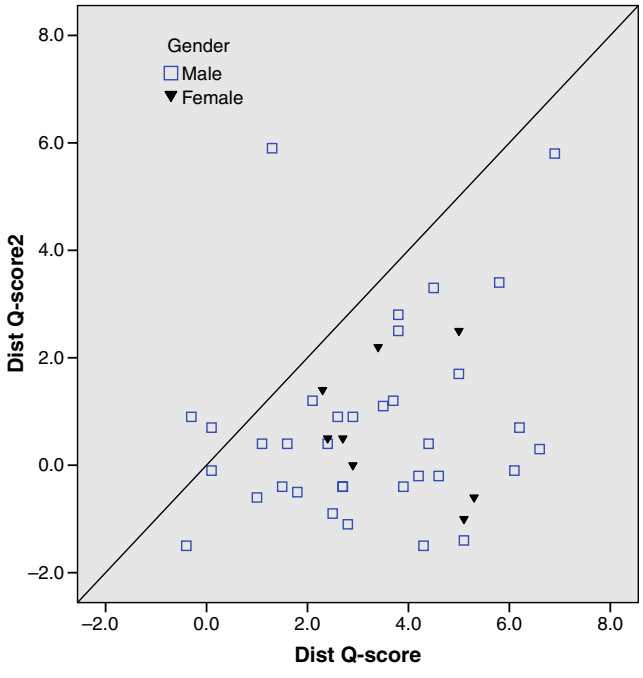

Figure 1. Increased and decreased total amount of activity between baseline and retesting on a moderate dose of methylphenidate. Distance Q-score and Distance Q-score2 indicate deviations from the population mean at baseline and at retesting on MPH. The cases below the diagonal line represent participants responding with decreased distance measures on MPH. The cases above the diagonal line represent participants responding with increased distance measures on MPH. Gender 1 = male; Gender 2 = female

administration and children receiving 7 days a week MPH.

By implementing a single dose protocol with a range of standard test conditions into clinical practice, a large, significant correlation between changes in activity and errors of omission was obtained. This result is consistent with the findings of Teicher et al. (2004). However, the correlation between activity changes and normalised reaction time variation, another attention parameter associated with a strong and reliable relationship to actual ADHD symptomatology (Epstein et al. 2003, Teicher et al.1996), was only moderate in our study. This result is likely to have been affected by those participants demonstrating a partial response or no response to a moderate dose of MPH.

Similarly a significant but only moderate correlation between changes in activity and errors of commission was found suggesting that in some cases the capacity to inhibit rapid responses may still be impaired despite reduced hyperactivity. This partial response to MPH formed a minority (7%) of cases with the majority of participants (84%) manifesting a robust treatment response on a moderate dose of MPH. Since a partial response is associated with an impulsive response profile (Teicher et al. 2004) this finding supports the suggestion of Hale et al. (2005) that children with more hyperactive/impulsive behaviours require a higher dose of MPH to establish a restoration of their neuropsychological impairment. However other factors, such as rapid metabolism may also be related to a partial response and further studies are required to evaluate the clinical effects of rapid metabolism on the response to MPH.

Elevated activity levels post MPH, in particular an increase in the distance value, has shown in this study to be a predictor for atypical responses to MPH possibly due to greater MPH sensitivity in cases with normal and borderline objective measures at baseline, cases of a predominantly inattentive type (Hale et. al., 2005) and an idiosyncratic response to psychotropic medication seen in children especially when co-morbid learning disabilities and behavioural disorders are present (Hale et al., 1998).

Study limitations and clinical implications

The normative data provided by QbTest/QbTest-Plus is based on 466 Swedish children and adolescents and is not referenced to a UK population. Therefore environmental, ethnical and cultural differences are not accounted for.

In comparison to CPT as a "stand alone" measure of attention deficits, the combined application of infrared motion analysis with CPT has demonstrated a significant and stronger correlation with common behavioural rating scales for ADHD completed by parents and professionals. According to Hale et al. (2005) most medication management strategies typically rely on behavioural observations and ratings in the classroom and at home to determine treatment effects and little attention is paid to the effects of medication on cognition when cognitive and behavioural domains can be affected differentially by medications even at the same dose (Hale et al 1998, Hoeppner et al 1997). Adding motion analysis/CPT into daily clinical practice provides valuable information in relation to both behavioural and neuropsychological medication responses with the capacity to detect partial as well as idiosyncratic responses to psychotropic medication. Further studies are required to assess how informed dose titration and dose monitoring through behavioural and objective neuropsychological evaluation will affect treatment outcomes more comprehensively bearing in mind that so far there is little evidence that the behavioural effects of MPH translate into academic gains (Purdie, Hattie & Carroll, 2002).

Conclusion

Initiating treatment with a moderate testdose of stimulant medication enables the early identification of treatment response (robust, partial and adverse treatment response) using objective measures of activity, attention and impulse control in children and young people diagnosed with hyperkinetic disorder seen in a generic CAMHS setting.

Most treatment responders demonstrated an effective response to MPH on a moderate testdose facilitating a swift and more optimal titration process.

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