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Clinical response to a single-dose methylphenidate challenge is indicative of treatment response at two months in adults with ADHD

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Stimulants such as methylphenidate (MPH) are the first-line pharmacological treatment for attention-deficit/hyperactivity disorder (ADHD). Although stimulants are effective at a group level, individual response varies, which advocates for tailored treatment approaches. Prior studies suggested that neurobiological measures following a single dose of stimulants are indicative of longer-term clinical response. To expand these findings, we tested whether an association between acute and longer-term treatment response can also be identified using measures commonly used in clinic. Sixty adults with ADHD completed clinico-neuropsychological measures, including the Barkley Adult ADHD Rating Scale-IV (BAARS-IV) and the Quantitative behavior (Qb) test, following a single dose of MPH (20 mg) and placebo. These measures were repeated after two-month MPH treatment to ascertain response. We tested associations between single-dose and longer-term response using univariate and multivariable (Lasso) regression approaches. We also ran correlations between predicted and true outcome measures. Univariate regressions showed significant associations between single-dose and two-month improvement in BAARS hyperactivity/impulsivity and Qb scores (all $p < 0.001$ but Qb activity, $p = 0.006$). Multivariable models including acute response and baseline clinicodemographic measures yielded significant correlations between predicted and actual values for all BAARS-IV and Qb scores at follow-up, except for BAARS inattention and Qb activity. Most had large/very large effect size (up to $r = 0.69$). These findings suggest that specific clinico-neuropsychological changes following a single dose of MPH may be indicative of longer-term treatment response, especially when combined with pre-treatment clinico-demographic characteristics. Once validated in larger and more heterogeneous samples, these results may support more informed and individualized treatment approaches for ADHD.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is defined by developmentally inappropriate inattentive and/or hyperactive-impulsive symptoms, and is one of the most common neurodevelopmental conditions [1, 2]. Prevalence ranges between 2–7% in childhood [3–5], and impairing symptoms persist in up to 75% of adults with childhood ADHD [6]. Stimulants, such as methylphenidate (MPH) and amphetamines, represent the first line pharmacological option [7, 8]. Stimulants ameliorate ADHD symptoms and associated cognitive deficits by modulating dopamine and norepinephrine neurotransmission in cortico-striatal brain networks, which promotes engagement of task-related brain networks, reduces interference from the default mode network, and increases perceived saliency [9, 10]. Fronto-striatal pathways have been the most investigated in ADHD [11–14]. These are GABA-glutamatergic circuits modulated by dopamine and contribute to cognitive, motor, and affective regulation by connecting the cerebral cortex to the basal ganglia and thalamus, which then projects back to the cortex [15–17]. These circuits contribute to executive functions and affect regulation, which are often affected in ADHD. Additionally, ADHD has been associated with noradrenergic pathways dysfunction. These originate from the locus coeruleus (LC), which is in the brainstem and is reciprocally connected with cortical regions, such as the prefrontal cortex. The balance between tonic and phasic noradrenaline release in the prefrontal

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cortex is crucial for optimal cognitive performance. Conversely, both excessive and insufficient stimulation negatively impacts on prefrontal functions and has been implicated in ADHD [10, 18]. By acting on catecholamine transporters, stimulants enhance endogenous dopaminergic stimulation and noradrenaline-dependent activation of post-synaptic receptors. Thus, they optimize prefrontal function by respectively reducing 'noise' and enhancing 'signal' within glutamatergic circuits, enabling effective 'top-down' regulation of response inhibition, attention, and motivation [10, 18–21]. Prescription rates of stimulants have been increasing in recent years, especially in adults. Data from the Massachusetts Prescription Drug Monitoring Program (PDMP) showed that stimulant prescriptions increased 70% from 2011–2021, with a tree-time increase in adults aged 35–44 years [22]. Similarly, the UK NHS Business Services Authority (NHSBSA) reported that prescription rates in 2022–23 increased by 32% in adults and 12% in children as compared to the previous year and that, as a result, stimulants were among the most prescribed psychopharmacological treatments (https://www.nhsbsa.nhs.uk/statistical-collections/medicines-used-mental-health-england/medicines-used-mental-health-england-201516-202223). Randomized controlled trials (RCTs) have clearly demonstrated superiority, at a group level, of both MPH and amphetamines over placebo across the lifespan [7, 8]. However, individual response varies, and this may negatively impact on outcomes, from educational attainment and occupation rates to substance misuse and legal offences [23, 24]. There is no current evidence to guide decision on which type of medication may be most beneficial for a specific individual. Indeed, in clinical practice, the most effective and best tolerated medication is selected using a trial-and-error approach, which may delay recovery and is not cost-effective [25, 26]. Therefore, there have been increasing efforts to identify pre-treatment characteristics associated with stimulant treatment response.

Considering pre-treatment clinico-demographic characteristics, prior studies have reported inconsistent findings. For instance, baseline symptom severity and intelligence quotient (IQ) have been reported to be either positively or negatively associated with treatment response [27–29]. Similarly, whilst some studies did not find an effect of age, others did [27, 29]. Comorbidities have been suggested to both reduce or not affect response [27, 30], although it has been noted that comorbidities are often inconsistently reported, when not excluded, in RCTs [30]. Treatment-related factors, such as dose and treatment adherence, appear to be more consistently associated with better response [27]. Considering neurobiological characteristics, neuroimaging and electrophysiological studies have suggested that brain characteristics, including anatomy of fronto-temporo-parieto-occipital regions [31]; fronto-parietal [32] and fronto-striatal connectivity [33, 34]; theta power [35, 36]; and P3 amplitude [36, 37], are associated with varying degrees of response to stimulants. These studies focused on pre-treatment (baseline) brain characteristics, but neurobiological studies also provided preliminary evidence that functional changes under a single dose of medication may be associated with longer-term treatment response [38]. For instance, changes in near-infrared spectroscopy (NIRS) signal under a single dose of MPH have been associated with better response at 4 weeks in children with ADHD [39]. Further, we observed that a single dose of MPH (versus placebo) increased resting state functional connectivity in three subcortical-cortical and cerebellar-cortical clusters, and that enhanced fronto-cerebellar connectivity was associated with a greater probability of responding to treatment in 56 adults with ADHD [40]. Similarly, more evident changes in P3 amplitude under a single dose of stimulants were associated with better longer-term response [37, 41]. Taken together, these findings suggest that neurobiological changes following a medication challenge may give an indication as to whether an individual will respond clinically post-dose optimization. To expand these findings, it would be helpful to understand whether medication challenge effects related to longer-treatment response can also be detected using measures commonly used in clinical practice (e.g., clinical scales).

In a systematic review of studies specifically investigating the association between acute and longer-term stimulant treatment response [42], we found only a secondary analysis of an RCT (among 63 single-dose identified studies) testing the association between acute and longer-term clinical response [29]. This study included 46 children (aged 6–13) with ADHD and reported that the improvement in clinical severity after a single dose of short-acting MPH (10 mgs) was significantly associated with clinical response at 4 weeks [29]. These preliminary findings are promising but, since that investigation only included children, may not necessarily apply to the adult population. In the present study we therefore tested whether changes in clinico-neuropsychological measures under a single dose of MPH were associated with treatment response post-dose optimization in adults with ADHD.

METHODS

Sample and research protocol

This study focuses on clinico-neuropsychological data collected as part of a larger neuroimaging trial (NCT 03709940). The original trial aimed at identifying brain characteristics, at baseline or under a single dose of MPH, that were associated with treatment response in adult ADHD. The trial included a within-subject single-dose placebo-controlled cross-over experimental phase, during which 60 adults with ADHD were tested both under a single dose of MPH and a single dose of placebo. This design is increasingly used in ADHD research and other fields as it allows to control for capsule order effects and participants' expectations on test performance [43, 44]. All participants then started longer-term treatment with MPH and treatment response was measured at two months (prospective open-label phase). The trial protocol and detailed inclusion/exclusion criteria have been previously described [32]. The selection of criteria was dictated by the need of the original trial to limit potential confounders to brain measures (see Limitations). We included 60 adults with a clinical diagnosis of ADHD according to the DSM-5 criteria [45], aged between 18 and 45 years, a full scale intelligence quotient (IQ) above 70, and no current comorbid disorders. The sample size ($N = 60$) was determined based on a power calculation, as reported in [31]; however, only 45 individuals completed the Barkley Adult ADHD Rating Scale-IV (BAARS-IV) under a single dose of MPH. Considering that ADHD is more commonly diagnosed in males [46], and there is preliminary evidence of sex differences in brain characteristics and biological response to stimulants [47–49], we only recruited males to enhance sample homogeneity. Most recruited participants were ADHD medication-naïve (see Results), and none had received any psychopharmacological treatment for at least a year prior to this study.

Our study included three sessions, two before starting routine treatment with MPH and one after two months of treatment to ascertain response. Before starting routine treatment, participants completed clinical and behavioral measures under placebo and under a single dose of 20 mg short-acting MPH. The first 30 participants received placebo first (session 1, baseline) and then MPH after 48 h wash-out (session 2, acute MPH). The order of the capsules was reverted for the second half of participants to balance any potential expectation and practice effect, and the protocol followed during the two sessions was identical to ensure blinding of participants (single-blind cross-over approach). The administered MPH dose (20 mgs) was slightly higher than the starting dose (15 mgs/day) recommended by the NICE guidelines (www.nice.org.uk), because 20 mgs were previously reported to affect brain activation in adults performing fMRI tasks [50]. Neuropsychological tests started one hour after MPH administration. The maximum plasma concentration (Cmax) after administration of immediate release MPH is attained in 90 min, with a 1-2 h range [50], thus the selected timing allowed participants to perform neuropsychological tests (and functional MRI scans not reported in the present study) under an optimal dose. After the two baseline sessions, participants received the same long-acting MPH formulation (Concerta XL, titrated up to 54 mg as per indications of the UK British National Formulary (BNF; https://bnf.nice.org.uk/drugs/methylphenidate-hydrochloride/)). Telephone follow-up appointments were offered during titration and the dose was adjusted if needed. Dose was considered as a covariate. Treatment

response (i.e., changes in clinico-neuropsychological measures at follow-up as compared to baseline) was measured at two months (session 3, follow-up). At follow-up, participants were also asked to complete an MPH assay to ascertain treatment adherence, however, results were analyzed in all participants according to an intention-to-treat approach.

At baseline, we measured IQ and handedness using, respectively, the Wechsler Abbreviated Scale of Intelligence (WASI) [51], and a modified version of the Edinburgh Handedness Inventory (EHI) [52]. Clinico-neuropsychological measures were acquired at each of the three timepoints. Clinical symptoms were measured using the BAARS-IV [53], which provides three scores (BAARS total, BAARS inattention, and BAARS hyperactivity-impulsivity). Participants also completed the Quantitative behavior (Qb) test (https://www.qbtech.com), a computer-based test that combines a continuous performance task (CPT) and infrared monitoring of an individual's movements to measure core ADHD symptoms. The Qb test measures several individual parameters to calculate three summary scores (Qb activity, Qb impulsivity and Qb inattention) (Supplementary Table S1). This test was granted approval from the Food and Drug Administration to support ADHD treatment monitoring [54]. More details on study protocol are reported in [32].

Statistical analysis

Univariate analyses. SPSS software (v29, IBM) was used to conduct the statistical analyses. Taking a dimensional approach, we first aimed to test whether a change in each of the three BAARS-IV scores, three Qb scores, or eight Qb individual parameters under a single dose of MPH (as compared to baseline) was associated with a change in corresponding measures at follow-up (as compared to baseline). For completeness, for the 6 main outcomes (three BAARS-IV and three Qb scores), we also tested associations between a change in each measure under a single dose of MPH and a change at follow-up in variables within the same set of analyses (e.g., whether an acute change in BAARS total score was significantly associated with a change in BAARS hyperactivity/impulsivity or BAARS inattention at follow-up). We first checked whether residuals followed a normal distribution through histograms and Shapiro-Wilk normality tests, and homoscedasticity through scatter plots. We then ran univariate regressions for outcomes that respected these assumptions and Spearman correlations for those that did not. Finally, we applied Bonferroni correction for multiple comparisons considering the number of variables in each set of analyses, each including different types of variables, i.e., we considered three BAARS-IV scores ($p < 0.016$), three Qb scores ($p < 0.016$), and eight Qb individual parameters ($p < 0.006$).

Machine learning: lasso regression. We then used Least Absolute Shrinkage and Selection Operator (lasso) regressions to identify which clinico-neuropsychological changes under a single dose (as compared to baseline) could predict changes in BAARS-IV and Qb scores at follow-up (as compared to baseline). Lasso regressions are a type of machine learning approach and are conceptually very similar to standard multiple logistic regressions but automatically select a limited set of independent variables. They can accept more variables than observations, even if collinear, as they use a regularization parameter to select a small set of independent variables with optimal prediction properties [55]. We specifically used the "easy.glmnet" R package [56] based on "glmnet" [57], which internally standardizes the variables so that they have unit variance. The machine learning analysis consisted of a single lasso regression model for each of the 6 main outcomes, which were the dependent variables (i.e., improvement in BAARS total score, BAARS inattentive score, BAARS hyperactive/impulsive score, Qb activity, Qb impulsivity and Qb inattention). The potential independent variables were the improvement in corresponding scores and Qb individual parameters under a single dose of MPH, as well as age, MPH dose, handedness, years of education, full-scale IQ, and baseline BAARS and Qb assessments. The lasso algorithm automatically selected the independent variables that best predicted the outcome. The algorithm automatically selects the predictors in a single step, without multiple testing, thus it does not require correction for multiple comparisons [55]. Further, lasso regressions do not estimate standard errors, for which assumptions required for correctly estimating the latter (e.g., collinearity) are unnecessary. However, we must clarify that in the presence of collinear variables, lasso may select one of the variables arbitrarily. Similarly, they do not infer p-values, for which assumptions needed for inference (e.g., a normal distribution of the residuals) are neither required. Rather, lasso regressions (and other machine learning algorithms) are evaluated by the accuracy of their predictions. For this reason, we conducted a leave-one-out cross-validation in which, iteratively, lasso was trained with all participants but one, and afterward, it was validated by assessing the accuracy of prediction in the remaining participants. In this leave-one-out cross-validation scheme, we fitted lasso regressions in the training sample to both impute (20 times) [58] the missing variables and create the prediction model. Afterward, we applied the imputation and prediction models to the test sample, thus testing them in individuals that have not been used in the analysis to create them, avoiding overfitting. Finally, we ran correlations between the predicted and the true outcome measures. We must note that we fitted 1200 instances of lasso for each prediction model (one for each of the 20 imputations of each of the 60 folds), but the "easy.glmnet" R package selected the model that was most similar to the other models according to the Dice coefficient [56].

Secondary analysis. Finally, to understand which IQ subscale may be more strongly associated with treatment response, we ran linear regressions where verbal or performance IQ were the independent variables and the outcomes for which we observed significant correlations between predicted and actual values at the lasso regressions were the dependent variables. For each outcome, we then considered which IQ component yielded the highest R^2. Details are reported in Supplementary Material, page 3.

RESULTS

Sample

Participants' mean (±SD) age was 28 (±7) years and full-scale IQ 109 (±12). On average, they had been in education for 14 (±2.3) years. Most of them were medication-naïve (77%) and right-handed (78%). At follow-up, most participants were on Concerta XL 54 mg as per protocol. The dose was modified in 34% of cases, mainly due to side effects, thus we considered dose as a covariate in the analysis (see Methods). MPH assay was negative at follow-up for 6 of the 55 available samples (i.e., 6 participants did not take MPH on the day of the follow-up) but all 60 participants were included in the analysis (intention to treat approach). Further details on sample characteristics, including data on individuals previously exposed to ADHD medication and their current level of response are reported elsewhere [32].

Statistical analysis

Univariate analyses. We first ran univariate regressions for the three BAARS scores (total, hyperactivity/impulsivity, and inattention) and the three Qb scores (activity, impulsivity, and inattention), for which assumptions were met (Fig. S1). We observed that an acute change in BAARS hyperactivity/impulsivity and in BAARS total score was significantly associated with a change in BAARS hyperactivity/impulsivity at two months (Table 1, Fig. 1). The former survived Bonferroni correction for multiple comparisons (N variables = 3, $p < 0.016$). Further, the degree to which each Qb score changed under a single dose of MPH was significantly associated with their degree of change at follow-up (Table 2, Fig. 1). All three associations survived correction for multiple comparisons (N variables = 3, $p < 0.016$). Conversely, the distribution of the residuals of most Qb individual parameters (i.e., Time Active, Distance, Area, Microevents, Omissions, Commissions, and Error rate) was not normal (Shapiro-Wilks $p < 0.005$, Fig. S1). We therefore conducted Spearman correlations. For all individual Qb parameters, but error rate, we observed that an acute change was associated with a change in the corresponding parameter at two months and survived correction for multiple comparisons (N variables = 8, $p < 0.006$) (Table S2).

Machine learning: lasso regression. As shown in Table 3, we observed significant correlations between predicted and actual values for all BAARS-IV and Qb scores at follow-up except for BAARS inattention and Qb activity. The corresponding effect sizes were small-medium for BAARS total score, and large-very large for BAARS impulsivity, Qb impulsivity and Qb inattention.

Table 1. Univariate regressions for BAARS-IV scores.

	Improvement BAARS-tot at follow-up		Improvement BAARS-ina at follow-up		Improvement BAARS-hyp/imp at follow-up	
Acute response	**Equation**	**F (p-value), R2**	**Equation**	**F (p-value), R2**	**Equation**	**F (p-value), R2**
	BAARS_ina_acute_response	Improvement	(fu) = 12.050 + 0.646BAARS_ina_acute_response	1.202 (0.279), 0.027	Improvement (fu) = 4.079 + 0.111 BAARS_ina_acute_response	0.500 (0.483), 0.011
Improvement	(fu) = 1.335 + 0.302BAARS_ina_acute_response	2.844 (0.099), 0.062				
BAARS_hyp/imp_acute_response	Improvement (fu) = 12.092 + 0.829BAARS_hyp/imp_acute_response	2.007 (0.164), 0.045	Improvement (fu) = 4.588– 0.070 BAARS_hyp/imp_acute_response	0.199 (0.658), 0.005	Improvement (fu) = 0.824 + 0.613BAARS_hyp/imp_acute_response	**14.709 (<0.001), 0.255**
BAARS_tot_acute response	Improvement (fu) = 12.169 + 0.138BAARS_tot_acute response	0.849 (0.362), 0.019	Improvement (fu) = 4.697-0.020BAARS_tot_acute response	0.256 (0.615), 0.006	Improvement (fu) = 0.937 + 0.098BAARS_tot_acute response	**4.875 (0.033), 0.102**

Linear regressions showed that changes in BAARS hyperactivity/impulsivity and total scores under a single dose of MPH were significantly associated with improvement in corresponding scores after two-month treatment (follow-up). The former survived correction for multiple comparisons. Symptom improvement at follow-up can be calculated according to the formula $Y = \alpha + \beta X$, where α and β are the constant and regression coefficient, and X the acute change of interest. Statistically significant results are displayed in bold.
BAARS Barkley Adult ADHD Rating Scale, *hyp/imp* hyperactivity/impulsivity, *ina* inattention, *fu* follow-up, *tot* total.

More specifically, improvement of BAARS hyperactivity/impulsivity at follow-up was associated with a change in BAARS hyperactivity/impulsivity and distance (a measure of activity) under a single dose of MPH, in a model controlling for baseline severity of hyperactivity/impulsivity symptoms, age, dose at follow-up, handedness, IQ and years of education. However, we must note that changes in distance, area, microevents, and time active (all measures of activity), were strongly correlated (r = 0.86–0.95), for which it is possible that lasso may have selected one or another arbitrarily. Improvement of BAARS total score was associated with a change in area under a single dose of MPH, in a model controlling for baseline total and inattentive symptoms, baseline Qb activity, dose at follow-up, handedness, IQ, and years of education. Improvement of Qb impulsivity was associated with changes in Qb impulsivity, omissions and error rate under a single dose of MPH, in a model controlling for baseline severity of total and inattentive symptoms, baseline Qb impulsivity and inattention, age and IQ. Finally, improvement of Qb inattention was associated with changes in Qb inattention, BAARS inattention, microevents, omissions and RT variability (measures of inattention), and error rate under a single dose of MPH, in a model controlling for baseline Qb impulsivity, age and IQ (Table 3).

Secondary analysis. Finally, we observed that the associations between total IQ and improvement in BAARS total score and in Qb inattention were driven by performance IQ, whilst the associations between total IQ and improvement in BAARS hyperactivity/impulsivity and Qb impulsivity were driven by verbal IQ (Table S3).

DISCUSSION

We provided proof of concept that specific changes in clinico-neuropsychological measures following a single dose of MPH were associated with treatment response after dose optimization in adults with ADHD. We observed that a change in BAARS hyperactivity/impulsivity scores or Qb scores under a single dose of MPH was associated with their change at the two-month follow-up. The same applied to individual Qb test parameters, and additional significant associations were noted, primarily among parameters within the same ADHD domain. These findings suggest that clinico-neuropsychological changes under a single dose, especially in Qb tests scores/parameters, may be reliable indicators of the degree of change in corresponding measures post-dose optimization. In addition, the lasso regressions showed significant correlations between predicted and actual values for most of the BAARS-IV and Qb scores at follow-up, with small-medium to large-very large effect sizes. Overall, our findings indicate that the acute response to a single dose of MPH contains valuable information about the probability of responding longer-term, especially when combined with other individual and treatment characteristics (e.g. baseline severity, MPH dose, and IQ).

Our results are in line with and expand those from the only prior RCT by Buitelaar et al. (1995) exploring the relationship between single dose and longer-term clinical response in children with ADHD [29]. That study was a secondary analysis of a double-blind RCT of MPH vs placebo in 46 children with ADHD, aged 6–13 years. It reported that an improvement in Clinical Global Impressions Scale (CGI) scores under an acute dose of MPH predicted symptom improvement after 4 weeks of MPH treatment, with an accuracy of 70%. When combined with baseline clinicodemographic measures, such as IQ, younger age and classroom inattentiveness, improvement after a single dose was the strongest predictor for symptom improvement (but not recovery) and enhanced the overall accuracy of the model. Our study adds to these prior findings as we observed significant associations between acute and longer-term response in adults with ADHD and also included neuropsychological measures.

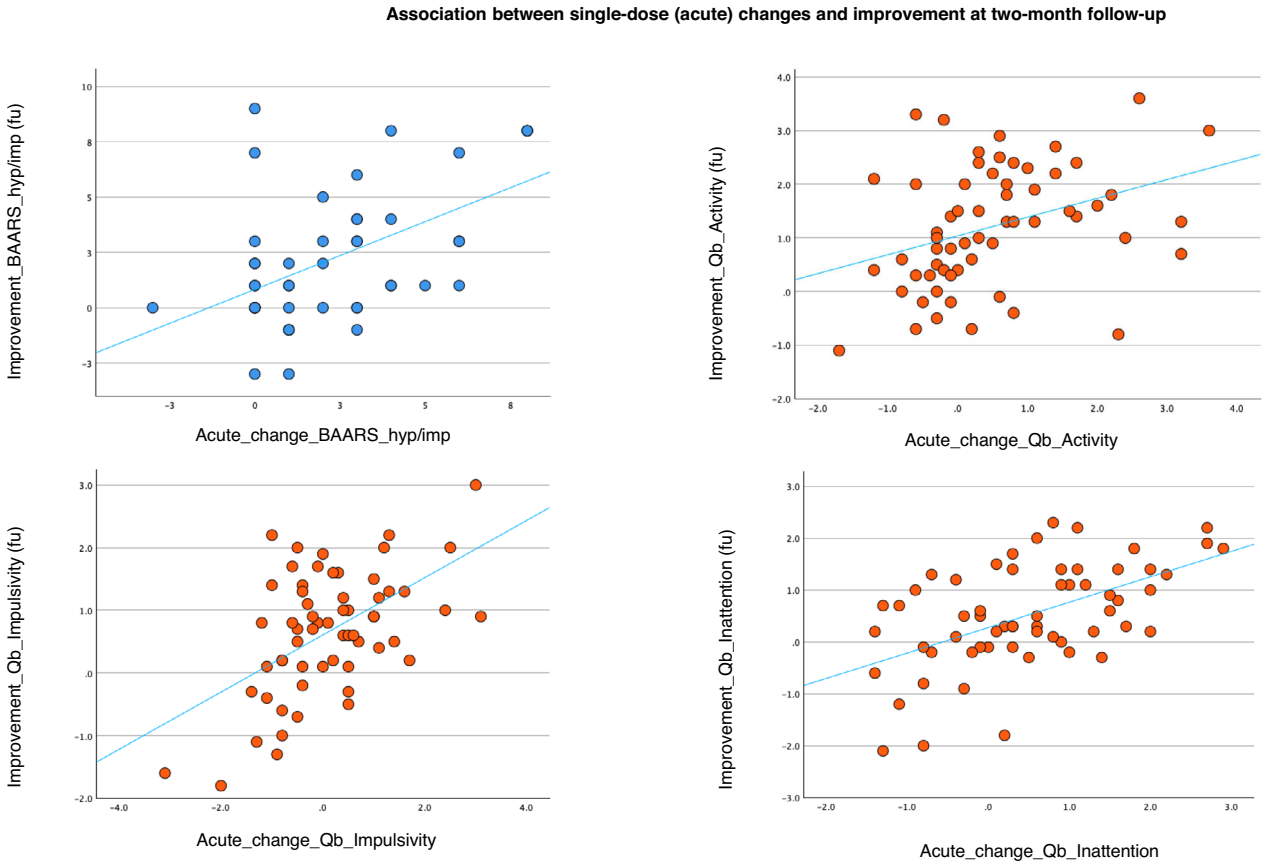

Fig. 1 Association between single-dose (acute) changes and improvement at two-month follow-up. These plots show the statistically significant results of the univariate regressions after Bonferroni correction for multiple comparisons. Changes in BAARS hyperactivity/impulsivity and Qb scores under a single dose of MPH were significantly associated with improvement in corresponding measures after two-month treatment (follow-up). BAARS hyp/imp Barkley Adult ADHD Rating Scale hyperactivity/impulsivity score, fu follow-up, Qb Quantitative behavior test.

Nevertheless, we did not observe a significant association between acute and longer-term response for all tested measures, such as inattentive symptoms. This suggests that certain ADHD symptoms might be less susceptible to single-dose MPH effects and/or individuals with ADHD may be less able to detect their acute change [59]. Further, our and prior findings support the utility of combining measures of acute response with pre-treatment clinico-demographic characteristics. For instance, total IQ was positively associated with improvement at two months in BAARS hyperactivity/impulsivity, BAARS total score, Qb impulsivity and Qb inattention. An association between higher IQ and better clinical response has been highlighted by some but not all previous reports [27, 28]. Regression analyses with IQ subscales suggest that visuo-spatial abilities may be more relevant to treatment-related improvement in attentive functions. This is in line with findings from our prior imaging study showing that the anatomy of the left dorsal attentive network, which is involved in the voluntary control of visuo-spatial information, was predictive of treatment response in adult ADHD [32]. Further, verbal abilities have been implicated in the mental representation of a task/complex behavior, which enables optimal execution and decision-making. For instance, a functional connectivity study reported that brain regions supporting language functions contributed to matrix reasoning performance in neurotypical controls [60]. Further, right-handedness was positively associated with improvement in BAARS hyperactivity/impulsivity and BAARS total score. Previous studies reported both no difference or higher rates of left-handed individuals among those with ADHD compared to neurotypicals [61, 62]. As reported in [32], 22% of adults with ADHD in our sample, but only 10% of controls, were left-handed. Although the mechanisms linking cognitive levels and handedness to treatment response are not known, these findings and those of prior studies suggest that treatment response is affected by the brain anatomical and functional organization on which stimulants act [32]. We also observed that age was positively associated with improvement at two months in BAARS hyperactivity/impulsivity and Qb impulsivity, but negatively associated with improvement in Qb inattention. The RCT by Buitelaar et al. noted that younger age was associated with better response [29]. Comparability between this and our study is limited as they included young children (below 13 years of age) and we included adults. Nevertheless, increasing age in ADHD is known to be associated with less evident hyperactive/impulsive symptoms [8]. We can therefore speculate that brain circuits supporting hyperactivity or inattention may be differentially susceptible to MPH effects with age. Finally, baseline symptom severity, cognitive performance and MPH dose may also be relevant, as supported by previous studies [27, 63, 64]. Taken together, these findings suggest that measures of acute response to MPH may be informative of longer-term response, especially when combined with baseline clinico-demographic characteristics.

The results of our lasso regressions also suggest that that there is not a precise correspondence between BAARS and Qb tests scores measuring the same symptom domain. For instance, we identified characteristics significantly associated with improvement in Qb inattention but not in BAARS inattention. We also noted significant associations for BAARS hyperactivity/impulsivity and for Qb impulsivity, but not for Qb activity. These discrepancies

Table 2. Univariate regressions for Qb scores.

	Improvement QbAct at follow up		Improvement QbImp at follow-up		Improvement QbIna at follow-up	
Acute response	**Equation**	**F (p-value), R2**	**Equation**	**F (p-value), R2**	**Equation**	**F (p-value), R2**
QbAct_acute response	Improvement (fu) = 1.037 + 0.350QbAct_acute response	**8.195 (0.006), 0.124**	Improvement (fu) = 0.636 + 0.059QbAct_acute response	0.267 (0.608), 0.005	Improvement (fu) = 0.445 + 0.143QbAct_acute response	1.596 (0.212), 0.027
QbImp_acute_response	Improvement (fu) = 1.183 + 0.227QbImp_acute_response	3.322 (0.074), 0.054	Improvement (fu) = 0.608 + 0.457QbImp_acute_response	**23.584 (<0.001), 0.289**	Improvement (fu) = 0.507 + 0.077QbImp_acute_response	0.474 (0.494), 0.008
QbIna_acute_response	Improvement (fu) = 1.097 + 0.233QbIna_acute_response	3.128 (0.082), 0.051	Improvement (fu) = 0.635 + 0.062QbIna_acute_response	0.277 (0.601), 0.005	Improvement (fu) = 0.277 + 0.490QbIna_acute_response	**23.786 (<0.001), 0.291**

Linear regressions showed that changes in the three Qb scores under a single dose of MPH were significantly associated with improvement in corresponding scores after two-month treatment (follow-up). All survived correction for multiple comparisons. Score improvement at follow-up can be calculated according to the formula $Y = \alpha + \beta X$, where α and β are the constant and regression coefficient, and X the acute change of interest. Statistically significant results are displayed in bold.
Act activity, *Imp* impulsivity, *Ina* inattention, *fu* follow-up, *Qb* Quantitative behavior test.

may be explained by the fact that the Qb test uses a CPT to detect alterations in sustained attention and response inhibition, which are not specific to ADHD, and may thus capture constructs that are partially distinct from clinical scales. In line with this suggestion, a neuropsychological study reported that ADHD symptom scales were able to differentiate between children with ADHD or autism but performance at the CPT could not [65]. Further, although these cognitive functions are involved in the completion of tasks and activities, rating scales such as the BAARS might capture more complex and 'real-life' behaviors. Nevertheless, both measures may be important for monitoring treatment response. For instance, a moderate significant correlation has been reported between improvement in Qb scores and quality of life at 6 months [66]. Finally, our models suggests that objective measures (e.g., Qb parameters) may be more sensitive to capture changes under a single dose of MPH than symptom scales due to the direct effects of the medication on neural activity [32], which may not reflect into immediate behavioral changes. These suggestions are supported by a recent systematic review of 15 studies using the Qb test. That review confirmed the ability of the Qb test to measure ADHD core symptoms on a behavioral level, but also highlighted a weak association between clinical scales and Qb scores [67]. For instance, a study including 145 adults with ADHD reported significant but small correlations between self-rated symptoms and Qb test scores both at baseline and after a month-treatment [68]. Similarly, a study including 78 children reported moderate significant positive correlations only between change in Qb test impulsivity and change in total and hyperactivity symptom measures after one-month treatment [69]. Of note, another study showed that subjective and objective measures of hyperactivity were correlated only in neurotypicals but not in individuals with ADHD, thus suggesting a different ability to report their activity levels [59]. Taken together, our and prior findings suggest that symptom scales and Qb scores may capture partially different ADHD-related constructs [68].

Overall, our study provided proof of concept that the response to a single dose of medication, measured using clinico-neuropsychological tools, may provide an indication as to whether an individual will respond clinically post-dose optimization. Future research should also investigate the mechanisms underlying the association between single-dose changes at the neurophysiological level and long-term clinical outcomes. For example, although we did not record electrophysiological measures in our study, previous research found that increased P300 (P3) amplitude – after a single dose of stimulant medication – predicted better longer-term clinical response [36, 37]. This finding is of interest because the P300 is a neural marker of attention orienting towards sensory stimuli and information processing [70], and has been found reduced in amplitude in individuals with ADHD [71]. Single-dose changes in the P300 and other neuro-physiological markers of attentional/behavioral regulation (e.g., heart rate variability) may therefore be tested as objective markers of long-term clinical outcomes in future studies [72]. Furthermore, considering recent evidence of changes in the P300 after transcranial electrical stimulation combined with cognitive training [73], it would also be important to understand if single-dose changes in electrophysiological measures predict long-term responses to non-pharmacological or combined interventions in those with ADHD.

The main strengths of this study are the longitudinal design and the use of clinico-neuropsychological measures that are often used in clinical practice to monitor treatment response. Nevertheless, limitations should also be considered. Regarding sample selection, inclusion and exclusion criteria were dictated by the need of the original neuroimaging study [32]. Prior studies suggested that sex differences exist in brain networks [74–76] and biological response to MPH [77]. However, it is not known how these aspects may interplay, thus we wanted to avoid potential sex-related confounding in our imaging analysis.

Table 3. Lasso regressions.

Improvement at two-month follow-up	cor	p	Equation
Improvement_BAARS_ina	−0.167	0.203	Improvement_BAARS_ina = 3.31 + 0.179 * BAARS_ina_baseline
Improvement_BAARS_hyp/imp	**0.497**	**0.000**	Improvement_BAARS_hyp/imp = −4.258 + 0.126 * BAARS_hyp/imp_acute response + 0.032 * Distance_acute_response + 0.525 * BAARS_hyp/imp_baseline + 0.033 * Age − 0.013 * Dose_fu + 0.061 * Handedness_score − 0.059 * Education_years + 0.022 * IQtot
Improvement_BAARS_tot	**0.284**	**0.028**	Improvement_BAARS_tot = 0.123 + 0.013 * Area_acute_response + 0.713 * Barkley_Ina_baseline + 0.247 * Barkley_tot_baseline − 1.065 * QbAct_baseline − 0.093 * Dose_fu + 0.177 * Handedness_score − 0.497 * Education_years + 0.083 * IQtot
Improvement_QbAct	0.126	0.337	Improvement_QbAct = 0.247 + 0.02 * QbAct_acute_response + 0.07 * QbImp_acute_response + 0.008 * Area_acute_response + 0.057 * Error_rate_acute_response + 0.22 * QbAct_baseline - 0.01 * Handedness_score + 0.007 * IQtot
Improvement_QbImp	**0.484**	**0.000**	Improvement_QbImp = −0.066 + 0.388 * QbImp_acute_response − 0.005 * Omissions_acute_response+ 0.047 * Error_rate_acute_response+ 0.024 * BAARS_Ina_baseline − 0.014 * BAARS_tot_baseline + 0.224 * QbImp_baseline - 0.092 * QbIna_baseline + 0.003 * Age + 0.007 * IQtot
Improvement_QbIna	**0.698**	**0.000**	Improvement_QbIna = −1.225 + 0.023 * BAARS_ina_acute_response + 0.311 * QbIna_acute_response + 0 * Microevents_acute_response + 0.013 * Omissions_acute_response + 0.12 * Error_rate_acute_response + 0.003 * RTvar_acute_response − 0.047 * QbImp_baseline - 0.01 * Age + 0.015 * IQtot

The lasso regressions showed significant correlations between predicted and actual values for BAARS total and hyperactivity/impulsivity, and Qb impulsivity and inattention with small-medium to large-very large effect sizes. Statistically significant results are displayed in bold.
Act activity, *Cor* correlation coefficient (r), *Imp* impulsivity, *Ina* inattention, *fu* follow-up, *p* p-value, *Qb* Quantitative behavior test.

Nevertheless, there is increasing recognition that, although ADHD is more commonly diagnosed in males in clinical samples, its prevalence in the adult general population is similar between males and females [46, 78]. Thus, we encourage further studies to extend our findings to the ADHD female population. Similarly, we only included individuals with no current comorbid conditions because neurobiological differences exist between individuals with/without comorbidities [79]. For example, recent meta-analyses highlighted both specific and shared connectivity alterations in individuals with ADHD and Autism Spectrum Disorder (ASD) [80, 81]; and individuals with both conditions have lower response to stimulant treatment [82]. Considering that our neuroimaging study was the first to investigate the association between connectivity and treatment response in adults with ADHD, we wanted to avoid potential comorbidity-related confounding. Nonetheless, the results of the current study should be validated in clinical samples also including individuals with comorbidities. Finally, we included a relatively small percentage of participants previously exposed to ADHD medication (23%). Pharmacotherapy is commonly prescribed in adults with ADHD, who may also concurrently use other psychopharmacological treatments [83, 84]. We made this choice because prior imaging studies reported that exposure to ADHD medication was associated with a 'normalizing' effect on brain structure [85]. Although other reports did not confirm this finding [86], we wanted to limit potential effects related to previous exposure to medication on our anatomical measures. Similarly, we had to exclude participants currently taking other psychopharmacological treatment to avoid confounding effects when measuring changes in brain functional connectivity induced by a single dose of MPH [40]. Thus, inclusion/exclusion criteria responded to the needs of the original imaging trial this study originates from. Nevertheless, although the findings provided by the current study provide a valuable proof of concept, they should be validated in more heterogenous samples.

Regarding study design, the original sample size ($N = 60$) was determined based on a power calculation, however, only 45 individuals completed the BAARS-IV under a single dose of MPH. Thus, results based on this measure should be considered as a proof of concept and need replication in larger samples. Further, placebo and MPH capsules were administered in a single-blind non-randomized prefixed order. In fact, the study was *not* conceptualized as a clinical trial of an investigational medicinal product (CTIMP), aiming at the comparison between medication and placebo effects on symptoms and cognitive functions, as superiority of MPH over placebo is well established [7]. Our study instead investigated whether an acute response to medication was predictive of longer-term treatment response. Thus, our study design was appropriate to our research question. Further, to limit potential sources of bias, placebo and medication were over-encapsulated using the same red opaque capsules; the protocol followed during the two sessions was identical; and symptom rating scales were complemented with objective measures of treatment response, based on the Qb test. Nevertheless, future studies may want to replicate findings using a more rigorous double blind RCT approach to single-dose testing. Considering the choice of treatment response measures, we opted for clinical scales and Qb test scores/parameters. This enhances the potential clinical utility of the identified models. However, other measures may also be considered. For instance, our recent systematic review identified 63 studies testing the effects of a single dose of stimulants using a variety of cognitive, neuroimaging, or neurophysiological measures [42]. Although not all these measures may be applicable to clinical practice in terms of cost-effectiveness, or related to longer-term response, further investigations on such variables may help understand the mechanisms underlying response to stimulants. Incorporating a broader set of variables, including clinico-demographic, neurophysiological, neuroimaging, and genetic factors, may also improve predictive accuracy of the proposed models. To this purpose, neurophysiological measures of stimulant effects on the activity of the central and peripheral (autonomous) nervous systems may be particularly helpful [87, 88]. In fact, it is known that MPH treatment increases blood pressure and heart rate [87]. Further, MPH can affect heart rate variability (HRV), i.e. the variation of heart rate over time. Notably, this measure of arousal and self-regulation has been associated with attention performance [89], but potential associations between acute changes in this measure and treatment-

related effects on ADHD symptoms or quality of life need further investigation [90, 91].

Considering our lasso regression models, these were instrumental to provide proof of concept that clinico-neuropsychological measures of treatment response under a single dose of MPH were associated with response post-dose optimization in adults with ADHD. However, we only conducted cross-validation as a means of internal validation but did not have an independent sample for external validation. Predictive models can often perform well on the data they were trained on but may not generalize as well to new samples, due to overfitting or sample-specific characteristics [92]. Thus, external validation is needed to ensure generalizability and robustness of our findings, before testing their potential applicability in clinical practice [25]. Additionally, the utility of alternative modeling techniques could be explored, including other machine learning approaches (e.g., random forests or support vector machines), ensemble methods that combine multiple models, or non-linear models (e.g., deep neural networks) able to capture complex relationships among tested variables [93]. In sum, while the current models show promise, there is likely room for refinement and optimization to enhance their predictive power and reliability across diverse populations. These novel, although preliminary, findings should encourage further studies in the field, given the substantial clinical relevance of stratification approaches that can support more informed and individualized treatment decisions for ADHD [25, 26, 94].

DATA AVAILABILITY

The data that support the findings of this study are available from the authors (VP) upon reasonable request.

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AUTHOR CONTRIBUTIONS

All authors gave substantial contribution to the study. VP was responsible for study design, recruitment of participants, data acquisition and analysis, and writing up of the manuscript. JR contributed to the data analysis and writing up of the manuscript. HT contributed to the data analysis and revised the manuscript. MGA and AB contributed to writing up and critical revision of the manuscript. SC contributed to study design and critical revision of the manuscript. DM was responsible for funding and critical revision of the manuscript.

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COMPETING INTERESTS

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were performed in accordance with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Ethical approval REC number: 12/LO/0630. All participants provided written consent.

ADDITIONAL INFORMATION

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