

MPH enhances cognitive performance in adults with poor baseline capacities regardless of ADHD diagnosis

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We compare the view that the effect of Methylphenidate (MPH) is selective to individuals with Attention Deficit Hyperactivity Disorder (ADHD) with an alternative approach suggesting that its effect is more prominent for individuals with weak baseline capacities in relevant cognitive tasks. To evaluate these two approaches, we administered sustained attention, working memory, and decision making tasks to 20 ADHD adults and 19 healthy controls, using a within-subject placebo-controlled design. The results demonstrated no main effects of MPH in the decision making tasks. In the sustained attention and working memory tasks, MPH enhanced performance of both ADHD and non-ADHD adults to a similar extent compared to placebo. Hence, the effect of MPH was not selective to ADHD adults. Additionally, those benefitting most from MPH in all three task domains tended to be individuals with poor task performance. However, in most tasks individuals whose performance was impaired by MPH were not necessarily better (or worse) performers. The findings suggest that the administration of MPH to adults with ADHD should consider not only clinical diagnosis but also their functional (performance-based) profile.

Keywords: MPH, ADHD, attention, working memory, decision making

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Introduction

Methylphenidate is a common medical treatment for ADHD (1) and its neuro-cognitive effects were extensively studied in both adults and children with ADHD. These studies showed that MPH improves various aspects of executive function such as sustained attention, response inhibition, and working memory capacity (2-5). Studies of healthy adults showed as well a positive effect of MPH on the same cognitive aspects (6-8). Nevertheless, a prevailing assumption is that MPH is more beneficial to individuals with ADHD than to healthy controls (e.g., 2, 3, 6). We contrast this view with an alternative approach that the beneficial effect of MPH is most evident for individuals with weak baseline capacities in a given cognitive task.

MPH's mechanism of action has been previously explained: it increases extra-cellular levels of dopamine and norepinephrine by blocking their respective transporters (9, 10). As ADHD is characterized by dysfunction of dopaminergic transmission in fronto-striatal regions (9-10), it can be argued that the effect of MPH is specific to ADHD. Surprisingly, though, studies that have directly assessed the selective effect of MPH have not reliably supported this prediction. The straightforward way to address this research question is to compare the effect of MPH in two groups of participants – ADHD and non-ADHD – with similar demographic indices, in a two-by-two research design. To our knowledge only two studies employed such a comparison, where both ADHD and healthy groups are medicated (6, 11). Vaidya et al. (6) studied children's performance on a Go/No-Go task, either after MPH administration (in one session) or off MPH (in the other). The Go/No-Go task assesses response inhibition, which engages both frontal and striatal functions (12), and is considered to be impaired in ADHD (13). Their findings indicated that in an easy task version, improvement in performance was only observed for the ADHD group; yet in a more demanding task version, MPH increased performance of both healthy controls and ADHD individuals to the same extent. Agay et al. (11) examined adults with ADHD and healthy controls, who were randomly divided into two groups. One group received MPH and the other received placebo. A complex Go/No-Go task, the Test Of Variables of Attention (TOVA; 14) was performed after medication. The TOVA results showed no effect of MPH or diagnosis. Additionally, in a Forward Digit-Span test completed after medication participants

who received MPH performed better than those on placebo, regardless of whether they had ADHD or not. In light of these findings, we hypothesized that ADHD individuals would not benefit more from MPH than healthy adults in Go/No-Go tasks such as the TOVA and related decision tasks (25), as well as in working-memory tasks.

Going beyond these previous studies, we also simultaneously examined the role of baseline capacity in the effect of MPH. A variety of theories proposed that MPH acts as a “normalizer”, increasing the performance of low capacity individuals but decreasing the performance of those with high capacity in the relevant task (16-18). In support of this notion, individuals who performed poorly in a given domain benefitted more from MPH on that domain. This was found most extensively for working memory capacity (19, 20, though not in 18) but also for motor functions (16) and visual memory processing speed (20). Additionally, the dopamine receptor agonist bromocriptine was recently found to have a positive effect on reversal learning in individuals with low baseline striatal dopamine synthesis but a negative effect for those with high synthesis capacity (21). An alternative, though related, account is that when the ability to perform a given task is high, task performance tends to be relatively automatic and requires less cognitive control (22, 23) and is thus less affected by baseline level of dopamine and norepinephrine. Hence, poor task performers have greater potential for improvement with MPH, but MPH does not impair performance beyond an optimum point.

Using a within-subject double-blind placebo controlled trial we directly contrasted the three accounts concerning the adult subpopulations that benefit most from MPH: The argument that the effect of MPH is ADHD-dependent and the two accounts assuming that its effect is largest for individuals with poor task performance. To compare the latter two accounts we divided the participants into those who benefited from the administration of MPH in a given task, and those who did not. The normalizer account suggests a negative correlation between baseline performance and improvement with MPH among those who benefit from it; but it also suggests a positive correlation between baseline performance and reduced performance with MPH among those who do not benefit from it. The automaticity account predicts the former but not the latter association.

Materials and Methods

Participants. Thirty-nine adults between the age of 20 and 40 were recruited from the local community through advertisements asking for participation of individuals with ADHD and healthy adults in a research study about Ritalin. The study was approved by the local and national Institutional Review Board, and was also registered at the U.S. National Institutes of Health (NCT01124032). All participants consented and signed an informed consent. Exclusion criteria were age below 21 or above 50; pregnant or nursing women; people suffering from a disorder other than ADHD which might affect the studied parameters; people who cannot be given MPH due to medical reasons; and people incapable of performing the computerized tasks due to motor or sensory disabilities. Participants were asked to provide a letter from their family doctor stating their general health condition, and to undergo an ECG scan in order to rule out any cardiac problem. Participants who reported taking Ritalin or similar medicine were asked to refrain from taking it in the morning of the experimental session.

A diagnosis of ADHD was determined for 20 individuals after a clinical interview with a senior psychiatrist using DSM-IV-TR criteria, and after performing three well validated self reports (ASRS1-18, Wender UTAH, Conners' Adult ADHD Rating Scale). Five out of these 20 had prior ADHD diagnosis, five were treated with Ritalin in the past, and seven used Ritalin in the present, either continuously or occasionally. The remaining 19 control participants did not have a diagnosis of ADHD on the basis of the same interview with a senior psychiatrist and three self-report tests. None had prior diagnosis of ADHD, and two reported using Ritalin occasionally (without prescription).

The control participants were matched to the ADHD sample for gender. All participants had university education except for four participants in the ADHD group and four participants in the non-ADHD group. All thirty-nine participants were screened for current axis-1 psychiatric disorders using the Hebrew version of SCID-1, a DSM-based structured interview. The ADHD and non-ADHD groups did not significantly differ in age, gender, or years of education. They significantly differed in the number of inattentive symptoms ($F(1,37) = 40.57, p < 0.001$) and hyperactivity/ impulsivity symptoms ($F(1,37) = 35.33, p < 0.001$) on the ASRS self-report, as well as in Wender-Utah score ($F(1,37) = 35.17, p < 0.001$) and CAARS ADHD score ($F(1,37) = 104.55, p < 0.001$).

Participants arrived at the lab for two sessions. In each session they received an opaque capsule containing Methylphenidate (Ritalin) or placebo (sweetener) in a double-blind manner. The mean dosage was 0.28 mg/kg (SD = 0.06). This is at the lower bound of the therapeutic dosage used for ADHD, which is 0.3 to 0.6 mg/kg (24). Consistent with the pharmacokinetic half-life of MPH (about 2.5 hours; 25), testing started 60 minutes following the drug ingestion. Because of the randomized administration to sessions, twenty-three participants received MPH on their first session and placebo on their second session, and sixteen received placebo on their first session and MPH on their second session. This did not affect the analyses of variance, which used the Type 3 method. All participants were rewarded for their participation, and were also paid 1% of their earnings in the gambling tasks.

Measures. Participants first completed the Test Of Variables of Attention (TOVA; 14). This is a rapid Go/No-Go task in which predetermined target stimuli should be discriminated from distracting non-targets. TOVA overall score is considered a measure of sustained attention, and is a weighted average of three subscales: response time, d-prime (accuracy over time, which is mostly affected by commission errors), and response time variability.

This was followed by working memory tasks, which included the Forward and Backward Digit-Span task (26), and the Spatial Working Memory (SWM) task (27). In the SWM participants are instructed to find tokens hidden inside boxes spread on the screen, while attempting not to select a box in which they had previously found a square. The outcome measures are total number of search errors, and a strategy score determined according to whether the same sequence of boxes is repeatedly used in different searches.

Finally, we administered two versions of the Iowa Gambling Task (IGT; 15). In this decision task, participants repeatedly select among four decks of cards which yield monetary outcomes. Two of the decks are disadvantageous, producing larger gains but also larger losses, while the other two decks are advantageous, though yielding smaller gains. The two task versions included the original version of the task (15) and a simplified version with a feedback method called foregone payoffs (11) wherein participants see the outcomes not only from the chosen deck but also from the other three decks. This task version will be referred to as the Foregone Payoff Gambling Task (FPGT).

Analysis. Our main analysis used a mixed ANOVA, with drug (MPH vs. Placebo) as the within subject variable, and diagnosis (ADHD vs. Non-ADHD) and order (Placebo before or after MPH) as between subject variables. All analyses were conducted in SPSS and used a p-value criterion of 0.05 (two tailed). The effect of baseline capacity was studied by correlations between performance on placebo and the effect of MPH among those who improved or did not improve with MPH.

Results

Go/No-Go task. As shown in Figure 1, the administration of MPH improved the TOVA score of ADHD individuals but also that of controls. Across session orders, the TOVA total scores (which are Z-scores) in the MPH condition were raised by 1.31 SDs for ADHD individuals and by 0.57 SDs for healthy controls. Two extreme observations with 3 SDs below average (one for a control participants and one for a participant with ADHD) were excluded and do not appear in the figure. The results of a repeated measures ANOVA revealed a significant main effect of drug ($F(1,33) = 4.48, p = 0.042$) and no main effect of diagnosis ($F(1,33) = 1.35, p = 0.25$). There was no interaction between the effect of the drug and ADHD diagnosis ($F(1,33) = 0.70, p = 0.41$). Finally, there was a significant interaction of drug by session order ($F(1, 33) = 19.6, p < 0.001$). Post hoc t-tests showed that MPH enhanced performance when it was given in the second session ($p = 0.001$), but when it was given in the first session, the effect was not significant ($p = 0.08$; see Figure 1, right pane). Importantly, neither the simple effect of MPH nor its combination with the order of experimental sessions interacted with the participants' diagnosis.

We also examined the correlation between baseline performance and the improvement with MPH (MPH-minus-placebo difference). As noted above, the correlation was conducted separately for those who improved with MPH ($N = 21$) and those for whom MPH impaired performance ($N = 16$). The results showed a significant correlation only in those who benefitted from MPH ($r = -0.46, p = 0.03$). For these individuals weak baseline performance predicted the amount of improvement with MPH. In the remaining subgroup of participants there was no significant correlation ($r = 0.19, p =$

0.66).¹ Hence, MPH did not normalize the performance of individual with high baseline capacity.

Working memory. The results for the Forward Digit-Span test are summarized in Figure 2 top panel.

There was no main effects of drug ($F(1,35) = 1.40$, $p = 0.24$) and no significant effect of ADHD diagnosis ($F(1,35) = 3.0$, $p = 0.09$). Instead, there was a significant interaction of drug by order ($F(1,35) = 10.08$, $p = 0.003$). Post hoc t-tests showed that performance was enhanced when MPH was given in the second session ($p = 0.007$), but not in the first session ($p = 0.14$; see Figure 2 right panel). Thus, the improvement from session to session was significant with MPH, but not with placebo. Importantly, again no interaction between ADHD and MPH administration was demonstrated ($F(1,35) = 0.001$, $p = 0.98$), as well as no three-way interaction of ADHD by drug by session order ($F(1,35) = 1.10$, $p = 0.30$). Interestingly, in the more demanding Backward Digit-Span test MPH there was no main effect of drug ($F(1,35) = 0.42$, $p = 0.52$) or diagnosis ($F(1,35) = 1.60$, $p = 0.21$), and none of the interactions were statistically significant. We therefore focus on the Forward version of the test in subsequent analyses.

For the Spatial Working Memory task, analysis of the number of search errors (Figure 2 middle panel) revealed a significant drug effect ($F(1,33) = 6.92$, $p = 0.01$), along with no significant effect of ADHD diagnosis ($F(1,33) = 3.55$, $p = 0.07$). Again, there was no significant interaction between the effect of the drug and ADHD diagnosis ($F(1,33) = 1.22$, $p = 0.28$). The only significant interaction was that of drug by order ($F(1,33) = 7.0$, $p = 0.01$). Similarly to the Digit-Span task, post hoc t-tests for each order revealed that performance was significantly enhanced for participants who began in the placebo condition and moved to MPH (mean number of errors was reduced by 60%, $p = 0.02$), but not for participants who moved from MPH to placebo (mean number of errors was not reduced, $p = 0.98$) (Figure 3 top right panel). For the strategy score there was a significant main effect of drug as well ($F(1,33) = 4.97$, $p = 0.03$; see Figure 2 bottom panel), with no effect of ADHD diagnosis ($F(1,33) = 0.62$, $p = 0.44$), or interaction between drug and diagnosis ($F(1,33) = 0.57$, $p = 0.45$).

We next examined the relation between poor performance and the beneficial effect of MPH. When examining the subgroup of participants who improved with MPH ($N = 21$ to 23 in the different

¹ We also conducted partial correlations controlling for session order, which yielded similar results.

tests), we found that the correlations were significant for the Forward Digit-Span test ($r = -0.57$, $p = 0.008$) and SWM errors ($r = 0.78$, $p < 0.001$). For the SWM strategy score the correlation was only 0.30 , $p = .19$, but this was due to an extreme observation, as shown by the significance of Spearman's non-parametric test ($\rho = 0.48$, $p = 0.03$). By contrast, for those whose performance was impaired with MPH ($N = 16$ to 19) the correlations were not significant: Forward Digit-Span test: $r = 0.095$, $p = 0.7$; SWM errors: $r = -0.22$, $p = 0.09$; SWM Strategy score: $r = 0.32$, $p = 0.23$).

Decision making. The results for the IGT appear in Figure 3 top panel. The analysis of variance showed only a main effect of ADHD diagnosis ($F(1,35) = 4.03$, $p = 0.05$). Participants in the ADHD group made disadvantageous choices on approximately 38% of the trials, compared to participants in the non-ADHD group who made such choices only on 31% of the trials. Apart from that, there was no significant effect of drug ($F(1,35) = 0.01$, $p = 0.92$) or interaction between drug and ADHD ($F(1,35) = 0.99$, $p = 0.32$). In the FPGT (Figure 3 bottom panel) there was no effect of drug ($F(1,35) = 0.39$; $p = 0.54$) or diagnosis ($F(1,35) = 0.63$, $p = 0.43$), and no interaction ($F(1,35) = 0.049$ $p = 0.83$).

Nevertheless, analysis of the IGT and FPGT data at the individual level showed that for the sub-group of participants who improved with MPH, improvement in performance was negatively correlated with performance level on placebo (IGT: $N = 19$; $r = -0.47$, $p = 0.04$; FPGT: $N = 15$; $r = -0.58$, $p = 0.02$). For those who did not improve with MPH, the performance change with MPH was also negatively correlated with performance level on placebo in the IGT ($N = 20$; $r = -0.72$, $p < 0.001$) though not in the FPGT ($N = 24$; $r = -0.14$, $p = 0.50$).

Discussion

Using a within-subject design, we examined whether individuals with ADHD or those with weak baseline capacity benefit more from MPH. Regarding the Go/No-Go TOVA task which is often used for diagnosing ADHD, the results showed a significant positive effect of MPH but no interaction between this effect and the participant's diagnosis. Instead, there was a significant positive association between poor baseline performance and improvement with MPH. The current findings thus seem to disprove a common heuristic popular among clinicians – 'if MPH improves TOVA score, then the

patient must have ADHD'. Instead, they show that 'if MPH improves TOVA score, then the person has poor initial capability in this test'.

Our findings for working memory tests likewise showed a remarkable similarity between adults with ADHD and healthy controls. Following MPH administration, an almost identical rate of improvement was recorded in performance scores of ADHD and healthy participants. By contrast, we have again found that the beneficial effects of MPH were larger for individuals with weak baseline capacities in the Forward Digit-Span task and in the SWM task.

By comparing the correlations among those who performed better or worse with MPH, we evaluated two explanations for this latter effect: one proposing a normalizing effect and the other proposing that for high performers the drug effect is independent from baseline attentional capacities (e.g., due to processes of automaticity). The results, though based on a relatively small sample, supported the latter explanation. The negative correlation between baseline performance and improvement with MPH was only significant for those who improved with MPH. This finding also suggests that the individual-level effect is not a by-product of regression to the mean. A regression to the mean would have led to negative correlations for those who improved with MPH as well as for those impaired by it (29).

The final cognitive domain that was examined was decision making. Our findings showed no performance-enhancing effect of MPH, as found previously (11). Also, consistent with our previous findings, among those who benefitted from MPH, weak baseline capacities were associated with a more positive effect. Yet in the Iowa Gambling Task, among individuals whose performance was impaired by MPH, high baseline performance was associated with reduced performance on MPH. This suggests a normalizing effect of MPH on decision making (see related finding in 30), though alternatively the same effect may be due to a regression to the mean.

To summarize, in all of the studied tasks the positive effect of MPH in healthy adults was similar to that observed for individuals with ADHD. Instead, individuals with weak baseline capacities benefitted more from the administration of MPH. This finding does not imply that MPH may not be appropriate for persons with ADHD. It suggests, though, that that individuals' functional profile should

be considered alongside their biological and psychiatric profile in order to determine the cognitive-enhancing effects of the drug.

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Figure 1: Results for the TOVA. Overall scores, averaged across sessions (left pane) and across groups (right pane). The right pane figure is ordered according to whether MPH was administered first (and placebo second) or second (and placebo first). The error bars represent the within-subject corrected standard error (28).

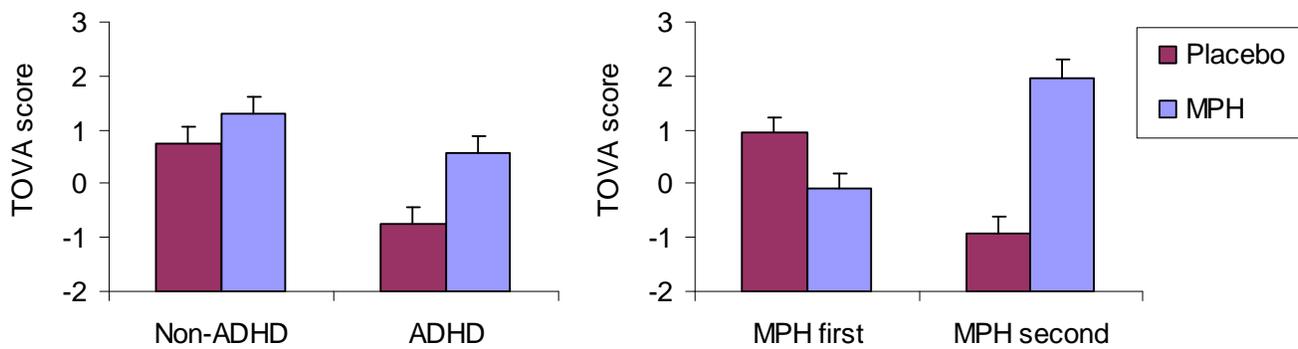


Figure 2: Results for the working memory tasks. Forward Digit-Span scores and Spatial Working Memory (SWM) scores (mean number of errors and strategy score), averaged across sessions (left panes) and across groups (right panes). The right pane figures are ordered according to whether MPH was administered first (and placebo second) or second (and placebo first). In the SWM measures, a low score denotes high performance. The error bars represent the within-subject corrected standard error (28).

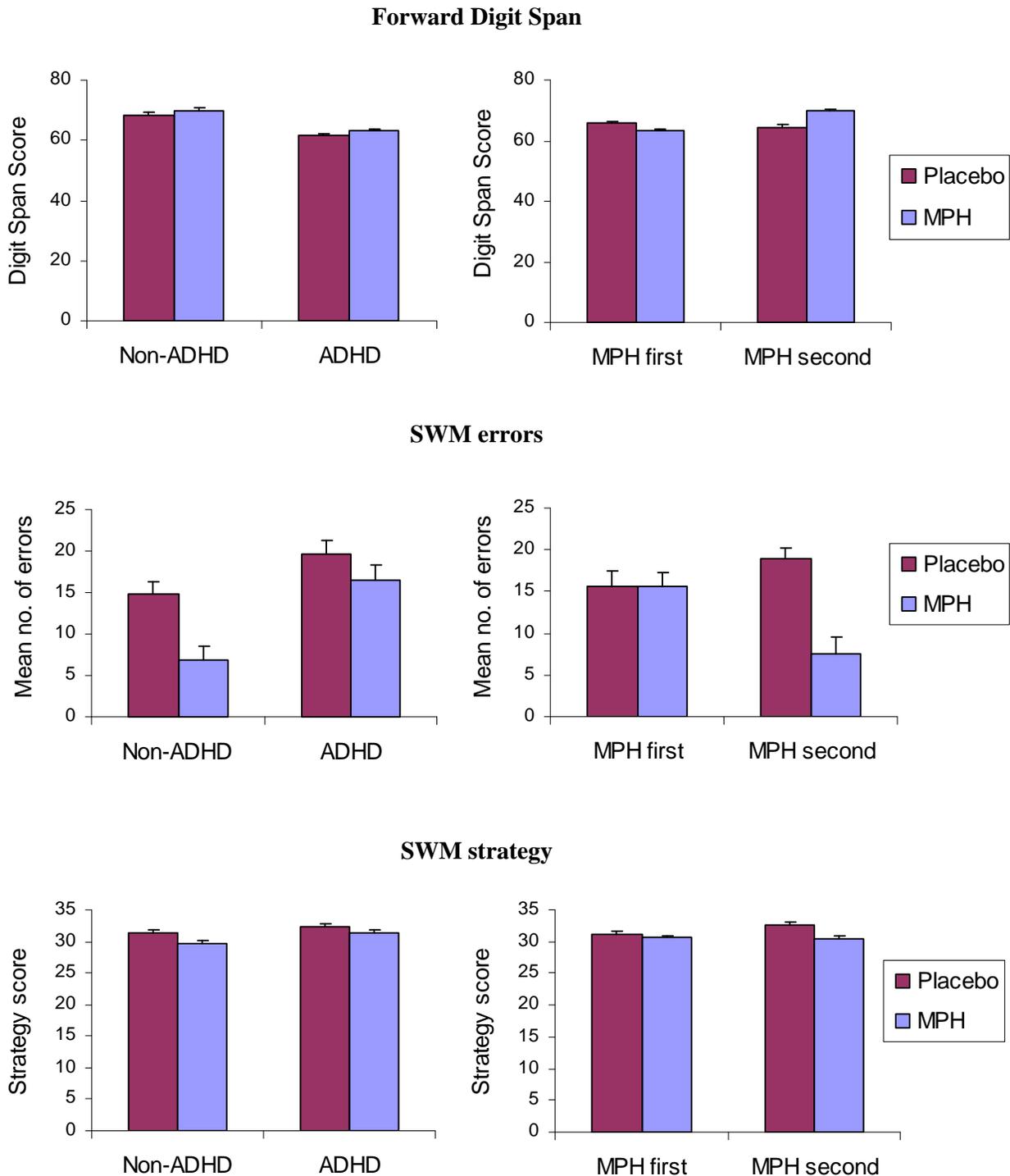


Figure 3: Results for the decision tasks: Disadvantageous selections in the Iowa Gambling Task (IGT) and in the Foregone Payoff Gambling Task (FPGT) by group and treatment, averaged across sessions. The score denotes the mean number of disadvantageous deck selections in 100 trials. The error bars represent the within-subject corrected standard error (28).

