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Methylphenidate does not enhance visual working memory but benefits motivation in macaque monkeys

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ABSTRACT

Working memory is a limited-capacity cognitive process that retains relevant information temporarily to guide thoughts and behavior. A large body of work has suggested that catecholamines exert a major modulatory influence on cognition, but there is only equivocal evidence of a direct influence on working memory ability, which would be reflected in a dependence on working memory load. Here we tested the contribution of catecholamines to working memory by administering a wide range of acute oral doses of the dopamine and norepinephrine reuptake inhibitor methylphenidate (MPH, 0.1–9 mg/kg) to three female macaque monkeys (*Macaca mulatta*), whose working memory ability was measured from their performance in a visual sequential comparison task. This task allows the systematic manipulation of working memory load, and we therefore tested the specific hypothesis that MPH modulates performance in a manner that depends on both dose and memory load. We found no evidence of a dose- or memory load-dependent effect of MPH on performance. In contrast, significant effects on measures of motivation were observed. These findings suggest that an acute increase in catecholamines does not seem to affect the retention of visual information per se. As such, these results help delimit the effects of MPH on cognition.

1. Introduction

Working memory is the ability to temporarily retain a limited amount of information for the guidance of thoughts and behavior. This basic cognitive process is thought to underlie our abilities in a variety of everyday tasks, including language, reasoning, and problem solving (Goldman-Rakic, 1990, 1995; Baddeley, 1992). Cognitive symptoms, including deficits in working memory, are characteristic of many psychiatric conditions, and are often treated with catecholaminergic drugs. The mechanisms by which such drugs affect cognitive processes, however, remain poorly understood.

Nonhuman primate models have been instrumental for the investigation of the neural mechanisms underlying working memory, including the contribution of catecholamines. A putative neural substrate of working memory has been identified in the persistent activity of neurons within the cerebral cortex of monkeys performing delayed response tasks (see for review Goldman-Rakic, 1995; Constantinidis and Wang, 2004; Khan and Muly, 2011). In such tasks, manipulating levels of catecholamines—dopamine (DA) and norepinephrine (NE)—have been reported to alter persistent activity with concomitant changes in working memory performance, primarily via action at DA D1 (DRD1) and NE alpha-2 (NRα2) receptors (see for review Arnsten, 2011; Cools and D'Esposito, 2011). These effects are generally described as following an inverted-U dose-response function, with excessively high levels associated with impairment.

Most of the neurophysiological evidence linking catecholamine modulation with changes in working memory originates from monkey studies using tasks requiring retention of a single memorandum. To fully establish a link between catecholamines and working memory performance, it is critical to test whether their effects depend on memory load. For example, studies using the DA and NE reuptake inhibitor methylphenidate (MPH) to manipulate catecholamine levels in monkeys have variously reported detrimental effects (Bartus, 1979), no significant effects (Bartus, 1978; Rajala et al., 2012; Soto et al., 2013; Hutsell and Banks, 2015), and enhancing effects on performance in single-memorandum delayed

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response tasks (Bain et al., 2003; Gamo et al., 2010). One potential reason for such equivocal results is the unaddressed possibility that catecholamine effects are most apparent when tasks are made more difficult by increasing mnemonic demands. Although there is a literature on the effects of MPH on healthy adult humans performing tasks requiring retention of multiple memoranda, evidence suggests marginal benefits (see for review Linssen et al., 2014; Ilieva et al., 2015), even though MPH continues to be used recreationally as a potential cognitive enhancer (McCabe et al., 2005, 2014; Smith and Farah, 2011; Ilieva et al., 2015). A major limitation of human studies is that MPH doses were generally not varied. Altogether, previous work has not systematically investigated effects of varying mnemonic demands across a wide range of MPH doses.

To address this gap in our knowledge, we administered orally a large range of MPH doses to three macaque monkeys performing a visual sequential comparison task. This task allows manipulation of mnemonic demand by varying the number of items which must be retained, and performance reflects directly the process of working memory retention (Luck and Vogel, 1997; Heyselaar et al., 2011). Using this approach, we sought specifically to determine whether catecholamines modulate task performance in a manner that depends on dose and memory load.

2. Materials and methods

2.1. Subjects and apparatus

Data were collected from three female rhesus macaques (*Macaca mulatta*; 5.0–8.0 kg; 12–14 years old). All animal care and experimental protocols were approved by the Queen's University Animal Care Committee and were in accordance with the Canadian Council on Animal Care guidelines. Animals were prepared for experiments by undergoing a surgery, in which a head restraint and subconjunctival search coils for monitoring eye position were implanted. The surgical details have previously been described elsewhere (Shen and Paré, 2006). Monkeys were paired housed in large enclosures (Clarence et al., 2006), and received antibiotics and analgesic medications during the post-surgery recovery period. Following recovery, animals were trained with operant conditioning and positive reinforcement to perform fixation and saccade tasks for a liquid reward. To ensure motivation, we regulated fluid intake by permitting the animals to obtain fluid only as reward during experimental sessions; fluid was provided in the enclosure on days off, including weekends. The animals thus worked for fluid until satiation, but were provided with daily fresh fruit and vegetable and unrestricted access to high protein monkey diet biscuit (product code 5045, Lab Diet, St. Louis, MO). The experimenters, the animal care staff, and university veterinarians closely monitored the animal's fluid intake, weight, and health.

The visual displays, behavioral paradigms, and data acquisition were controlled by the QNX-based Real-Time Experimentation Software (REX) system running on a Pentium III PC (Hays et al., 1982). Visual displays were generated by a display program using Matlab and the Psychophysics Toolbox (Brainard, 1997) running on a Power Mac G4 computer and presented on a 37" monitor (NEC MultiSync XP37 plus, 60-Hz non-interlaced, 800 × 600 resolution, 32-bit color depth) at a viewing distance of 57 cm. Eye positions were monitored using the magnetic search coil technique (Robinson, 1963). Field coils placed around the animal generated opposing horizontal and vertical magnetic fields, which allowed the recording of voltage proportional to the horizontal and vertical angular eye position generated from the scleral search coil.

Stimulus arrays consisted of two to five colored squares, each measuring 1.2° × 1.2°, presented at an eccentricity of 10° from a central fixation point. For each set size, the positions of the stimuli remained identical across trials. For set size two, the stimuli were located to the left and right of the fixation point. For all other set sizes, all stimuli were presented at equal distances, with one stimulus always presented directly above the fixation point. For each trial a set size was randomly assigned and colors for the stimuli were chosen at random from a library of six highly discriminable colors: red (CIE x = 0.633, y = 0.327, L = 9.8 cd/m^2), green (CIE x = 0.288, y = 0.602, L = 9.8 cd/m^2), blue (CIE x = 0.155, y = 0.063, L = 9.9 cd/m^2), magenta (CIE x = 0.345, y = 0.168, L = 9.9 cd/m^2), yellow (CIE x = 0.432, y = 0.485, L = 9.9 cd/m^2), or cyan (CIE x = 0.223, y = 0.337, L = 9.9 d/m^2). Luminance and chromaticity were measured using a Minolta CA100-Plus photometer. Each color could only appear once in a given display.

2.2. Behavioral paradigm

Monkeys performed a visual sequential comparison task (Heyselaar et al., 2011), commonly referred to as a change detection task (Fig. 1). Every trial started with the appearance of a white central fixation point (CIE x = 0.323, y = 0.325, L = 9.9 cd/m^2). They had 1000 ms to fixate on this stimulus and had to maintain fixation for 500–800 ms within a 2° × 2° window. Subsequently, a memory array composed of a randomly assigned set of two to five colored squares was presented for 500 ms. The duration of the memory array presentation was chosen based on previous experiments which showed that 500 ms are sufficient for the monkeys to perform this task accurately. The memory array was followed by a 1000 ms retention interval during which no stimuli, except for the central fixation point, were presented. Finally a test array appeared consisting of the original display but with one square a different color. Simultaneously, the fixation point was dimmed (L = 1.37 cd/m^2) and the monkey had to indicate within 500 ms which stimulus had changed by making a single saccade to its location. If she successfully identified the changed stimulus, a liquid reward was delivered directly to her mouth and the trial was marked as 'correct'. If she made a saccade that did not land on the changed stimulus or did not respond within 500 ms (omission), no reward was given, the trial was marked as 'incorrect', and was followed by a time out period of 3000 ms. If she aborted an ongoing trial by making a saccade away from the fixation window before the presentation of the memory array, this abort was considered a fixation break. If she aborted an ongoing trial during the presentation of the memory array, this was considered an array break. Finally, if she aborted an ongoing trial during the retention interval, this was considered a retention break. Between trials the monitor screen was illuminated with diffuse white light (1.5 cd/m^2) to prevent dark adaptation. The inter-trial interval was 1000 ms following correct trials and 3000 ms following incorrect trials.

The duration of the retention interval was chosen to correspond with that used in human studies with change detection tasks (Luck, 2008; Luck and Vogel, 2013). The rationale to use a retention interval relatively short, but beyond the duration of iconic memory, is to control for the impact of long-term memory storage. Similar task performance is observed in change detection tasks with longer intervals (3–8 s; Vogel et al., 2001; Jeneson et al., 2012), suggesting little decay of the memory representation over the course of several seconds. However, task performance in patients with damage to medial temporal lobe structures is selectively impaired for long retention intervals (3–8 s; Jeneson et al., 2012). In summary, there should be little or no impact of long-term memory on performance in the task that we implemented.

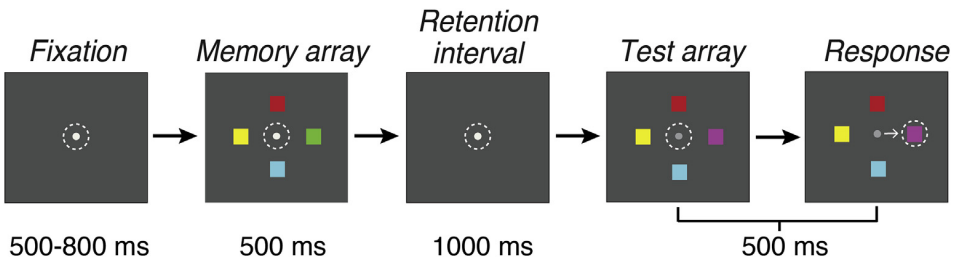

Fig. 1. Task design. Correctly performed set size four trial in the visual sequential comparison task. White dotted circle and arrow represent eye position and movement, respectively.

2.3. Experimental procedures

Prior to starting these experiments, all animals had performed at least 10,000 trials and showed stable performance on the task. Data regarding the performance on this task has been published previously for one of the animals (*monkey G*) used in this study (see for details Heyselaar et al., 2011). For each experimental session monkeys performed a minimum of 600 trials, which is equivalent to approximately 1 h of testing. A session was terminated when the animal consistently refused to initiate trials by not fixating the central fixation point for a prolonged period (approx. 2–5 min) and despite encouragement. This moment was occasionally also signaled by the animal being agitated. In a well-trained animal, this moment is readily identified and it closely corresponds to when the animal has received the amount of fluid for which she regularly works.

For a treatment session, they received an oral administration of MPH (Methylphenidate hydrochloride, Sigma-Aldrich, St. Louis, MO) 30 min prior to session start. This time frame was chosen as previous studies have shown that the blood peak concentration of MPH in rhesus macaques is reached after approximately 60 min (Doerge et al., 2000). MPH is a highly lipid soluble and readily crosses the blood-brain barrier. Previous studies have estimated that MPH concentration in brain structures also peaks within 1 h of oral administration in baboons (Ding et al., 2004) and humans (Spencer et al., 2006); similar figures are reported in rats after intraperitoneal injections (e.g., Bymaster et al., 2002). Rat studies have also demonstrated that the decline of MPH concentration in brain paralleled that in plasma (e.g., Segal et al., 1976).

Immediately prior to oral administration, MPH was mixed with vehicle. Juice was used as vehicle for one animal (*monkey M*). Applesauce was first used in the other animals (for approximately half the sessions) and then replaced by yogurt, because of compliance issues. Doses were chosen randomly prior to a given treatment day. All treatment sessions were compared to control sessions that were collected the day preceding the respective treatment session. Due to this procedure, we largely controlled for the potential effects of varying estrogen levels on working memory in female monkeys (Lacreuse et al., 2015). All experimental sessions were conducted at the same time for each animal. The days following a treatment session were marked as 'post-drug' days and data collected on those days was not included in this analysis. A maximum of two treatment sessions per week were collected, with at least two days in between treatments. A one-day washout period was deemed sufficiently long, because the elimination of MPH is fast. In monkeys, the half-life elimination is < 2 h, which means that there is no amount of the drug detectable in plasma after 12 h (Doerge et al., 2000). A mouse study has also shown that basal extracellular levels of cortical NA and DA are not affected by daily MPH (3-mg/kg) treatment (Koda et al., 2010).

The following doses were tested in all three animals: 0.1, 0.5, 1, 3, 6, and 9 mg/kg. In *monkey G* a larger number of MPH doses was tested, specifically in the range of clinically relevant doses (0.2–0.9 mg/kg; Pietrzak et al., 2006). These additional doses were 0.13, 0.18, 0.25, 0.35, 0.7, and 1.7 mg/kg. Previous non-human primate research mostly investigated doses ranging from 0.1 to 1 mg/kg (Bartus, 1979; Bain et al., 2003; Gamo et al., 2010; Hutsell and Banks, 2015), although both smaller (0.01–0.3 mg/kg; Soto et al., 2013) and higher doses (1.5–9 mg/kg; Rajala et al., 2012) have recently been tested. None of the three monkeys in this study had received any MPH prior to the experiments, and each animal received its respective MPH doses only once. Two of the monkeys used in this study (*monkey G* and *F*) had previously received doses of the NMDA antagonist ketamine as part of an experimental study (Shen et al., 2010).

2.4. Serum MPH level analysis

Measurement of the blood serum level of MPH was carried out using a commercial enzyme-linked immunosorbent assay technique (ELISA) following the manufacturer's instructions (Bioo Scientific Corp., Austin, Texas). Separate from this study experiments, blood was drawn from three animals (*monkey G* and *F* as well as from *monkey P*, from which no experimental data were collected) before administration of 1 mg/kg MPH, as well as 30, 60, and 90 min following administration. Analogous to experimental sessions, MPH was mixed with juice and administered orally. The samples were left to clot and sera were separated and either stored at −20 °C or used immediately for assay. All serum samples were assayed in duplicate in 96-well microplates. Absorbance values of each standard and the samples were measured at 450 nm using a VERSAmax tunable microplate reader (Molecular Devices, Sunnyvale, California). SoftMax Pro software was used to generate the best-fit plot of the standard curve. The detection limit was 0.5 ng/ml. MPH plasma concentration was measured 30, 60, and 90 min following oral administration and averaged across animals. The mean (±SD) concentration before administration was 1.7 ± 0.9 ng/ml, and all subsequent measures were found to be significantly greater [30 min: 13.3 ± 4.9 ng/ml (range 9.6–18.8); 60 min: 20.9 ± 5.8 ng/ml (range 17.2–27.6); 90 min 19.3 ± 7.4 ng/ml (range 13.7–27.7)].

These results indicate that this mid-range MPH dose yielded a blood concentration that was within the therapeutic range (5–20 ng/ml; Swanson and Volkow, 2003; Patrick et al., 2005) during the length of our experimental sessions. Positron emission tomography (PET) studies estimated that the majority of striatal DA transporters are occupied following oral administration of comparable doses in healthy adult humans (Volkow et al., 1998, 2002; Spencer et al., 2006). Complementary PET studies reported 10–20% increases in extracellular DA concentration in striatum (Volkow et al., 2001, 2002; Rosa-Neto et al., 2005; Clatworthy et al., 2009; Schabram et al., 2014) and cortex (Montgomery et al., 2007).

Lastly, it has been estimated that 70–80% NE transporters in subcortical structures are blocked by MPH following oral administration of therapeutic doses (Hannestad et al., 2010).

2.5. Data analysis

All experimental data were analyzed offline using MATLAB (The MathWorks, Natwick, MA). To assess the effects of MPH on working memory performance, response accuracy, defined as the probability that the first saccade landed on the target, and response latency, defined as the time between onset of the test array and initiation of the first saccade, were computed. Only the first 600 trials of every treatment and control session were analyzed. This ensured that the animals were similarly motivated during control and treatment sessions, as well as to keep the number of trials constant across animals. The total number of trials performed in each session varied within and between animals and generally was not much larger than 600—it averaged 725, 1152, and 791 trials in *monkey G*, *F*, and *M*, respectively. Each animal in this study participated in several experimental sessions under both control and treatment conditions. As such, a large number of trials were available for analysis: a minimum of 3600 trials under treatment and control conditions. To capitalize on the power of this data set, we additionally wished to pool sessions, where appropriate. Data across all control and across all treatment sessions were compared using a χ^2-test ($p < 0.05$). If there was no significant difference in either of the two groups, data from all sessions were pooled into treatment and control and compared using a χ^2-test ($p < 0.05$). If there was a significant difference within the treatment sessions only, control sessions were pooled and compared to every treatment session using a repeated χ^2-measure with a sequentially adjusted p-value (Holm, 1979). The same was the case if there was a significant difference within control sessions only. If there were significant differences within control and treatment sessions, each treatment session was compared to its corresponding control session in a pairwise manner (χ^2-test, $p < 0.05$). Effect sizes for χ^2-tests were described using ϕ or Cramér's *V*, depending on the number of comparisons, using the following formula:

$$\varphi/V = \sqrt{\frac{\chi^2}{N(k-1)}}$$

where *N* is the total number of samples, and *k* is the number of either rows or columns, whichever one is smallest (Cramér, 1946). If $k = 2$, then ϕ is calculated; if $k > 2$, then Cramér's V is calculated.

When evaluating response accuracy, only the trials labeled as either correct or incorrect were analyzed; trials that were aborted before the onset of the test array were excluded from the analysis. Omission errors were counted as error trials and included in the analysis, but they were not included in quantifying response time; the number of omission errors was negligible (0.07% of total errors). For visualization purposes, effects of MPH on response accuracy are shown as proportion correct as a function of dose for each set size (Fig. 3) as well as standardized change from the average control response accuracy (Fig. 4), which was obtained by subtracting the average control from the MPH response accuracy and dividing by the standard deviation of the control response accuracy.

To investigate differences in response latency between treatment and control sessions, we conducted two three-way ANOVAs. The first ANOVA was carried out to determine if a general effect of MPH on response latency was present and capitalized on the power engendered by the large number of trials carried out by each animal and by pooling data within treatment types. For this analysis all control and all treatment sessions were pooled and compared. If effects were present in this analysis, a second three-way ANOVA was run in which response latencies at each of the doses of MPH tested were compared to determine if any dose-dependent effects were present. Each three-way ANOVA included the factors condition (MPH vs. control in the first analysis, or MPH dose in the second), set size, and trial outcome (correct or incorrect). Post-hoc comparisons were done using Tukey's HSD test. We estimated effect sizes using Hays' omega squared (ω^2) (Hays, 1963; see also Skidmore and Thompson, 2013):

$$\omega^2 = \frac{SS_{effect} - df_{effect} * MS_{error}}{SS_{total} + MS_{error}}$$

where SS_{effect} is the sum of squares for the effect currently of interest, df_{effect} are the degrees of freedom for the effect currently of interest, MS_{error} is the mean squared error, and SS_{total} is the sum of squares for all effects, interactions, and errors in the ANOVA. For visualization purposes, effects of MPH on response latency are shown using standardized change (*d*, see equation below) from the average control response latency (Fig. 5). Effect sizes for t-tests were also estimated with Cohen's *d* calculated using the following formula:

$$d = \frac{[m(MPH) - m(Control)]}{\sigma(Control)}$$

where m is the mean and σ the standard deviation (Cohen, 1988; see also Glass, 1976). Standardized changes were additionally assessed using *t*-test ($p < 0.05$). All repeated tests were conducted with sequentially adjusted Bonferroni corrections (Holm, 1979).

We assessed the motivation of the animals with several measures of task engagement. As in Shen et al. (2010), we first compared the proportions of aborted trials across all trial intervals and within each trial interval using χ^2 tests ($p < 0.05$). Secondly, we assessed differences in the proportions of trials that the monkey failed to initiate (χ^2 test, $p < 0.05$), differences in the time they took to initiate a trial (rank sum test, $p < 0.05$) and differences in the proportion of trials in which the fixation point was already fixated at the time the trial started (χ^2 test, $p < 0.05$). Results were illustrated by showing the difference in task engagement measures as proportion ratio, computed as the proportion of trials with the respective measure in treatment sessions divided by the proportion of those trials in control sessions. Whenever the proportion ratio was shown to vary in a dose-dependent manner, we attempted to fit either a linear or a quadratic model. Finally, the total number of trials initiated in treatment sessions was compared to those in corresponding control sessions (paired *t*-test, $p < 0.05$). We had to omit from these analyses the 0.35-mg/kg treatment session and its corresponding control session in *monkey G*, because the allotted time for initiating a trial by fixating the central fixation point in this treatment session was inadvertently set to a different value (4000 ms) than for all other sessions (1000 ms). This difference had, however, no effect on measures of response accuracy or response latency.

3. Results

3.1. Control task performance

The visual sequential comparison task used in this study was adapted from human studies (Luck and Vogel, 1997; Luck, 2008) and previously described in Heyselaar et al. (2011), in which we documented the performance of two macaque monkeys. Here we tested the effects of MPH on task performance of three monkeys: one animal from our previous report (*monkey G*) and two additional

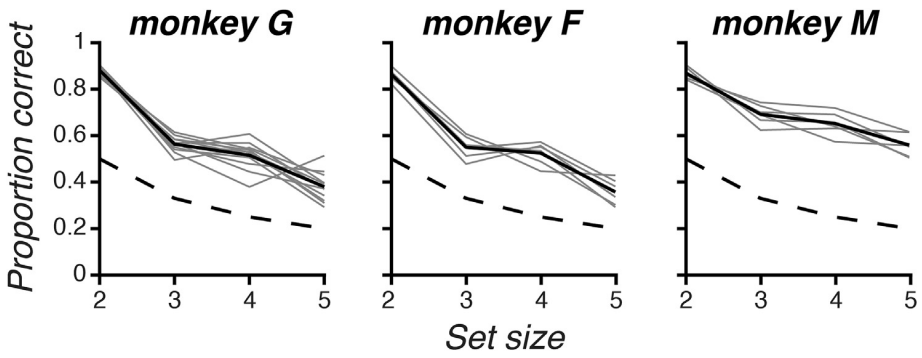

Fig. 2. Proportion correct as a function of set size. The mean proportion of correct responses is shown for all control sessions in each monkey; the overall mean is highlighted in black. Dashed lines represent chance performance (1/set size).

animals (*monkey F & M*). All animals received extensive training before entering this study. Proportion correct in control sessions yielded response accuracy similar to that reported in Heyselaar et al. (2011) (*monkey G*: 0.88, 0.56, 0.52 and 0.38; *monkey F*: 0.86, 0.55, 0.53 and 0.36; *monkey M*: 0.87, 0.70, 0.65 and 0.56 for set sizes two, three, four, and five, respectively) (Fig. 2). These proportions exceeded chance probability at all set sizes across all animals (z-test, $p < 0.0001$) and they significantly decreased as a function of set size (ANOVA, $p < 0.0001$). None of these proportions were too high to allow drug-induced improvements, especially for set sizes greater than two.

Response latency for correct and incorrect responses across all control sessions were assessed using a two-way ANOVA, with set size (two to five) and trial outcome (correct or error) as factors, followed with post-hoc comparisons. Response latency for *monkey G* was significantly longer on error trials compared to correct trials for set size two only (149 vs. 158 ms, $p < 0.05$). Response latency for *monkey F* was significantly longer on error trials for all set sizes (181 vs. 178 ms, $p < 0.05$). Response latency for *monkey M* was significantly longer on error trials only for set sizes three and five (174 vs. 161 ms, $p < 0.05$). These results indicate that the errors made by the monkeys were diligent guesses, made on the basis of mnemonic information rather than random responses (Link, 1982; Heyselaar et al., 2011).

3.2. Effect of MPH on response accuracy

Response accuracy following administration of MPH was compared with response accuracy from control sessions. For visualization purposes, Fig. 3 shows the proportion correct as a function of dose for each set size in each animal, and Fig. 4 shows standardized changes in response accuracy in treatment sessions following administration of MPH. Across animals, response accuracy in treatment sessions generally fell within two standard deviations of the average response accuracy in control sessions and there was no consistent dose- or memory load-dependent effect. For *monkey G*, response accuracies across all treatment sessions for each set size were not significantly different from each other (χ^2 test, $p > 0.20$; Cramér's $V < 0.1$). For set size four and five, response accuracies across control sessions were significantly different from each other (χ^2 test, set size 4: $p = 0.027$, Cramér's $V = 0.11$; set size 5: $p = 0.034$, Cramér's $V = 0.13$). Pooled data from all treatment and all control sessions for set size two revealed a significant difference (χ^2 test, $p = 0.016$, $\phi = 0.04$). For set size two, *monkey G* generally performed worse with MPH compared to control, but this effect did not follow a clear dose-dependent function. This statistically significant difference corresponds to a performance change of 2.7%, a difference that was likely rendered significant due to the large data set (≥3600 trials). Pooled data from all treatment and all control sessions for set size three revealed no significant difference (χ^2 test, $p = 0.16$, $\phi = 0.02$). For set size four and five, data from all treatment sessions were pooled and compared to single control sessions in a pairwise manner. No significant differences were found after correcting for multiple comparisons (repeated χ^2 test, sequentially rejective Holm-Bonferroni, $p > 0.05$, $\phi < 0.07$).

For *monkey F*, response accuracy within each set size and across control sessions did not differ significantly (χ^2 test, $p > 0.15$; Cramér's $V < 0.11$), but response accuracy across all treatment sessions for set size two differed significantly (χ^2 test, SS2: $p = 0.019$, Cramér's $V = 0.12$). For set size two, all control sessions were pooled and compared to individual treatment sessions. Compared to control, only the response accuracy at the 3-mg/kg MPH dose was significantly different; *monkey F* performed significantly worse with MPH compared to control performance (repeated χ^2 test, sequentially rejective Holm-Bonferroni, $p = 0.0074$; $\phi = 0.08$). For the set sizes three to five, comparison between pooled treatment and pooled control sessions did not reveal any statistically significant difference (χ^2 test, $p > 0.08$; $\phi < 0.04$).

For *monkey M*, no statistically significant difference was found in response accuracy within each set size and across control or treatment sessions (χ^2 test, $p > 0.05$, Cramér's $V < 0.12$). Comparison between pooled treatment and pooled control sessions did not reveal any significant difference (χ^2 test, $p > 0.10$, Cramér's $V \leq 0.1$).

Overall, MPH showed minimal effects on response accuracy for all doses and set sizes tested, with most effects found only at single doses or single set sizes. A dose-dependent or memory load-dependent effect of MPH on response accuracy in the visual sequential comparison task was not observed. This was the case for all three animals.

3.3. Effect of MPH on response latency

Mean response latency varied between control sessions, between treatment sessions, and between control and treatment sessions. These differences were, however, marginal and inconsistent across animals. Most importantly, the changes in response latency following treatment did not follow any coherent dose-dependent function.

The effect of MPH on response latency was first assessed with a three-way ANOVA—with treatment (drug vs. no-drug), set size, and trial outcome (correct vs. incorrect) as factors. A statistically significant main effect of treatment on response latency was observed in all animals, but the size of this effect was very small. Response

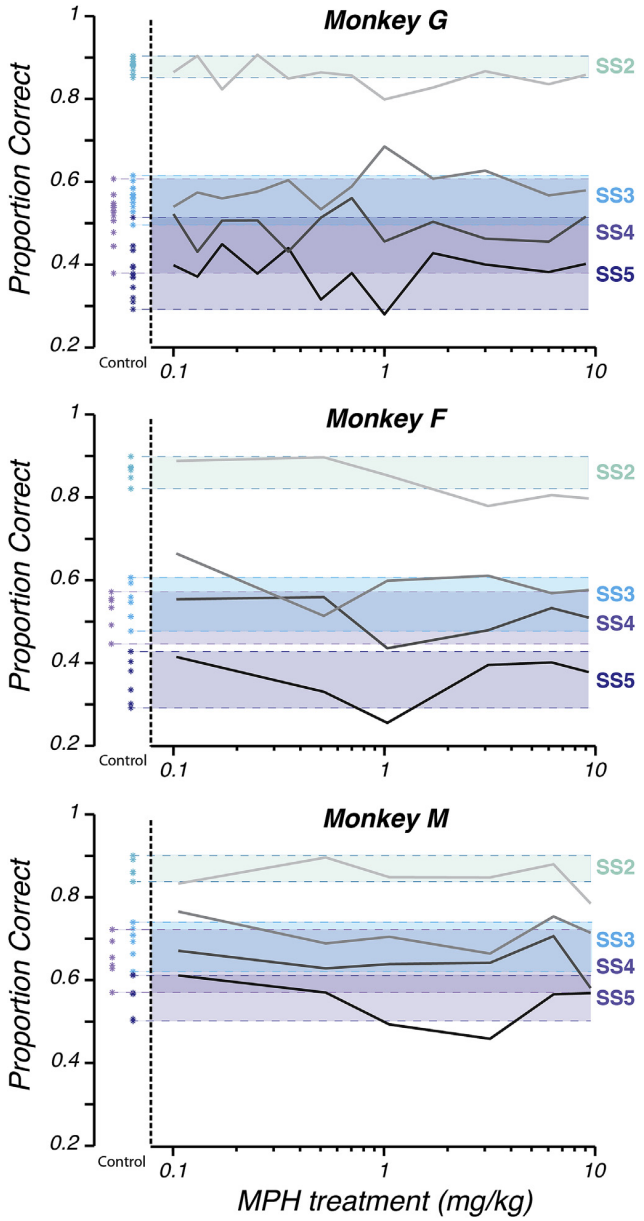

Fig. 3. Proportion correct as a function of MPH dose. Grey lines represent proportion correct as a function of MPH dose for each set size in each animal. Stars on the left side of each plot indicate proportion correct in every single control session. Dotted lines and shaded areas indicate range of proportion correct observed in control sessions. Set sizes are indicated on the right.

latency in two animals was significantly longer in control sessions than following MPH (*monkey G* and *F*: $p < 0.001$; $\omega^2 = 0.003$), whereas the converse was observed in the other (*monkey M*: $p < 0.001$; $\omega^2 = 0.006$). A significant interaction between treatment and set size was only found in *monkey F* ($p < 0.005$; $\omega^2 = 0.001$); response latency in set size four and five trials was significantly longer in treatment session than in control sessions (Tukey HSD test, $p < 0.01$). An interaction between treatment and trial outcome was not observed for any of the animals ($p > 0.19$). A significant interaction between set size and trial outcome was observed in *monkey F* ($p < 0.005$; $\omega^2 = 0.002$) and *monkey G* ($p < 0.001$; $\omega^2 = 0.0045$); when present, differences were such that response latency was longer on error than correct trials, as reported previously (Heyselaar et al., 2011).

Given the main effect of treatment found, we assessed the effect of MPH dose on response latency with a second three-way ANOVA with dose, set size, and trial outcome as factors. This second ANOVA revealed a significant, though small, main effect of dose on response latency in all animals ($p < 0.001$; ω^2 range 0.007–0.017). Nevertheless, for none of the animals did the effect of dose on response latency show a distinct pattern, and changes relative to control data were inconsistent across doses and animals.

Fig. 5 illustrates the standardized changes in latency for the correct responses made by each animal at each set size. Across monkeys, standardized changes in response latency following treatment generally fell within 2 SD of the average response latency observed in control sessions. The effect size (Cohen's *d*) across doses and set sizes averaged 0.10, 0.14, and −0.11 for *monkey G*, *F*, and *M*, respectively. Similar effect sizes were obtained for standardized changes in response latency relative to the mean response latency observed in corresponding control sessions (0.12, 0.15, and −0.09 for *monkey G*, *F*, and *M*, respectively). Fig. 5 also depicts the few statistically significant differences within set sizes that were detected with repeated t-tests ($p < 0.05$) with sequentially rejective Holm-Bonferroni corrections. There was no evidence supporting the hypothesis that MPH shortens response latency, with the exception of the highest dose in *monkey M*, but this was not associated with improved response accuracy (Figs. 3 and 4). Across set sizes, only the 3- and 9-mg/kg doses in *monkey M* were found to yield response latencies statistically shorter than control. In summary, in none of the animals did we observe evidence supporting a dose-dependent modulation in response latency.

3.4. Effect of MPH on response latency variability

Variability in response latency, a potential measure of the ability to stay on task and that is considered to be modulated by NE activity (Stuss et al., 2003; Aston-Jones and Cohen, 2005; Murphy et al., 2011), has previously been reported to be reduced by administration of MPH (Nandam et al., 2011). As an additional measure of performance, we therefore examined the effect of MPH on response latency variability using the coefficient of variability (standard deviation divided by the mean response latency). None of the monkeys used in this study showed an effect of MPH on the coefficient of variability of response latency (*t*-test, $p > 0.14$), which averaged between 0.15 and 0.22 for correct responses across animals.

3.5. Effect of MPH on saccade parameters

There are known catecholamine inputs to the primate superior colliculus (e.g., Morrison and Foote, 1986; Camps et al., 1990), a structure providing crucial driving signals to the brainstem saccade generator (Hanes and Wurtz, 2001); NE inputs from bilateral projections of the locus coeruleus to the brainstem omnipause neurons have also been reported in the cat (Ito et al., 1984). Consistent with these potential influences, MPH has been reported to affect saccadic eye movements (see for review Allman et al., 2012). We therefore examined the effect of MPH on metrics and kinematics of all correct saccade responses by measuring the following parameters: saccade amplitude, saccade peak velocity, and saccade acceleration and deceleration durations. Across monkeys, none of these parameters was found to change significantly following MPH (*t*-test, $p > 0.25$).

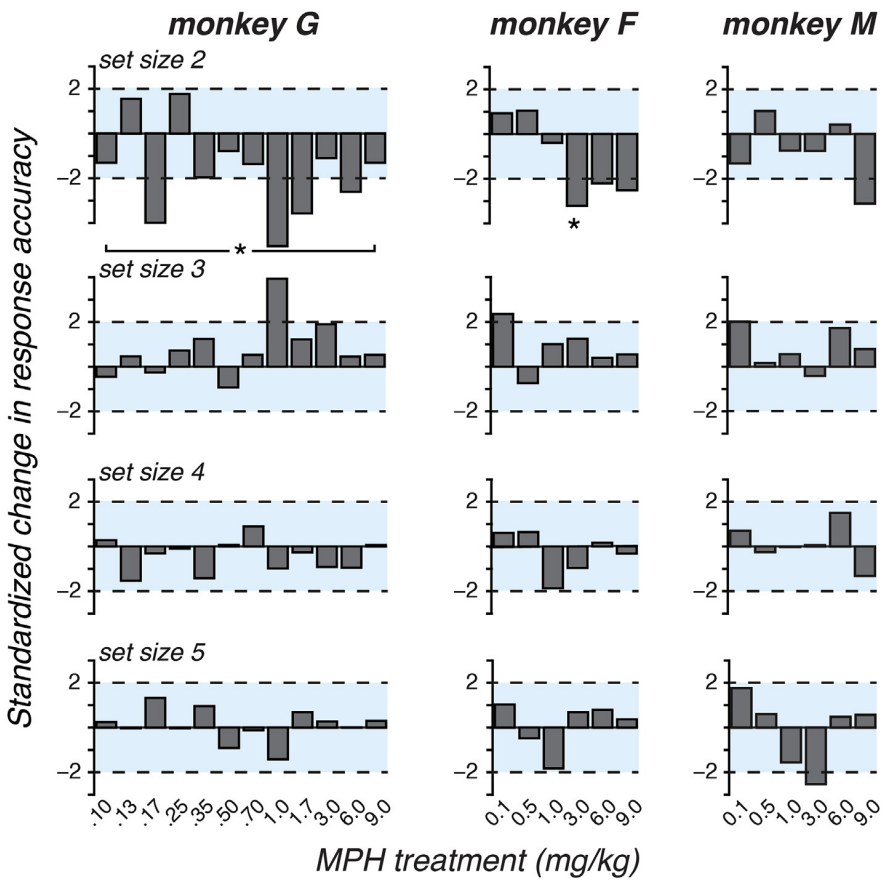

Fig. 4. Standardized change in response accuracy following MPH administration. Standardized difference is calculated relative to the average response accuracy across control sessions. Units are SD and the dashed horizontal lines indicate ±2 SD from the control average. Independent of dose, *monkey G* performed significantly worse in treatment sessions for set size 2 (χ^2 test, $p < 0.05$). *Monkey F* performed significantly worse for set size 2 following 3-mg/kg MPH (χ^2 test, $p < 0.05$).

3.6. Effect of MPH on task engagement

We first investigated the potential effects of MPH on task engagement by comparing the proportion of trials that were not completed (i.e., aborted) between treatment and control sessions (Shen et al., 2010). The proportion of aborted trials across all sessions and monkeys averaged 5% of the total trials. Considering all possible types of aborted trials, only *monkey G* aborted significantly fewer trials with MPH compared to control (χ^2 test, $p < 0.001$, $\phi = 0.11$; *monkey F*: $p = 0.11$, $\phi = 0.019$; *monkey M*: $p = 0.79$, $\phi = 0.003$). Fig. 6 shows the proportion of aborted trials between treatment and control sessions for each animal **(***top***)** as well as the ratio between the two in relation with MPH dose **(***bottom***)**. In *monkey G*, this proportion varied with dose (χ^2 test, $p = 0.002$, $\phi = 0.065$), and this effect reached statistical significance in seven (out of eleven) treatment sessions (repeated χ^2 test, sequentially rejective Holm-Bonferroni, $p < 0.05$). In *monkey F*, this proportion did not vary with dose ($p < 0.25$, $\phi = 0.043$) and no session showed significantly fewer aborted trials with MPH. In *monkey M*, this proportion did vary with dose (χ^2 test, $p < 0.001$, $\phi = 0.14$), but no session showed significantly different proportion of aborted trials following MPH; the 0.5-mg/kg dose failed to reach significance ($p = 0.024$, $\phi = 0.065$). We also examined the effect of MPH on different types of aborted trials. Again, only *monkey G* committed significantly fewer fixation, array, as well as retention breaks (χ^2 test, $p < 0.001$). *Monkey F* and *M* showed no significant effect on the proportion of aborted trials for any break type (χ^2 test, $p > 0.12$).

In any task, animals do not always initiate every single trial. In our study, failure to fixate the fixation point within the allotted time (1000 ms) could reflect reduced task engagement. We therefore computed the proportion of trials that failed to be initiated and tested whether it was lower in treatment sessions than in control sessions. Across doses, *monkey G* failed to initiate only 4.4% of treatment trials compared to 17.4% of control trials (χ^2 test, $p < 0.0001$, $\phi = 0.20$). The other two monkeys did not show a proportion of trial initiation failures that were significantly lower in treatment than in control sessions (*monkey F*: 0.04 vs. 0.042, $p = 0.71$, $\phi = 0.004$; *monkey M*: 0.092 vs. 0.076, $p = 0.011$, $\phi = 0.029$). Within each monkey, however, that proportion varied with dose (χ^2 test, $p < 0.0001$, $\phi = 0.14$–0.32). This is illustrated in Fig. 7 (*top*), which shows the ratio between the proportion of trial initiation failures in treatment and corresponding control sessions as a function of MPH dose. Improvement (ratio <1) was statistically significant in six (out of eleven) treatment sessions in *monkey G* (repeated χ^2 test, sequentially rejective Holm-Bonferroni, $p < 0.05$) and in one out of six (the 1-mg/kg dose) in both *monkey F* and *monkey M*.

As a secondary measure of trial initiation performance, we also computed the time that each monkey took to initiate fixation on the fixation point in each trial. The distribution of these trial initiation times was non-normal, as many trials started with the animal's gaze already at the fixation point. These data were therefore analyzed with non-parametric statistics. In both *monkey G* and *F*, the distribution of trial initiation times was generally shorter in

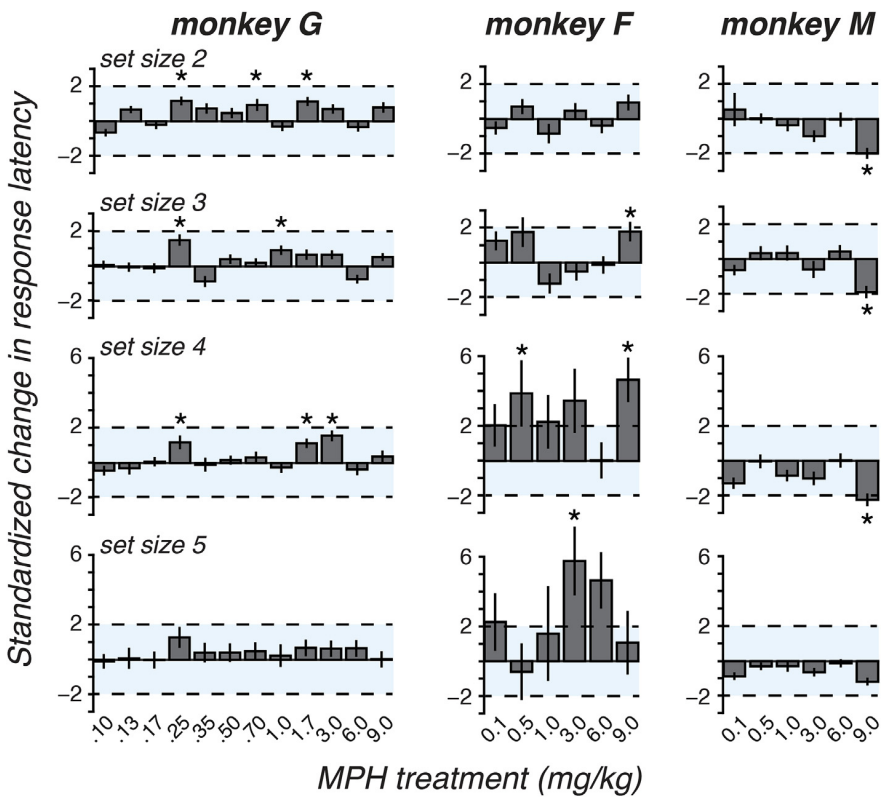

Fig. 5. Standardized changes in response latency following MPH administration. Standardized difference is calculated relative to the average response latency across control sessions. Units are SD and the dashed horizontal lines indicate ±2 SD from the control average. Average response latency across control sessions was 160 ± 27 ms in *monkey G*, 178 ± 26 ms in *monkey F*, and 161 ± 33 ms in *monkey M*. Error bars, 95% confidence intervals. Asterisks, statistically significant changes ($p < 0.05$).

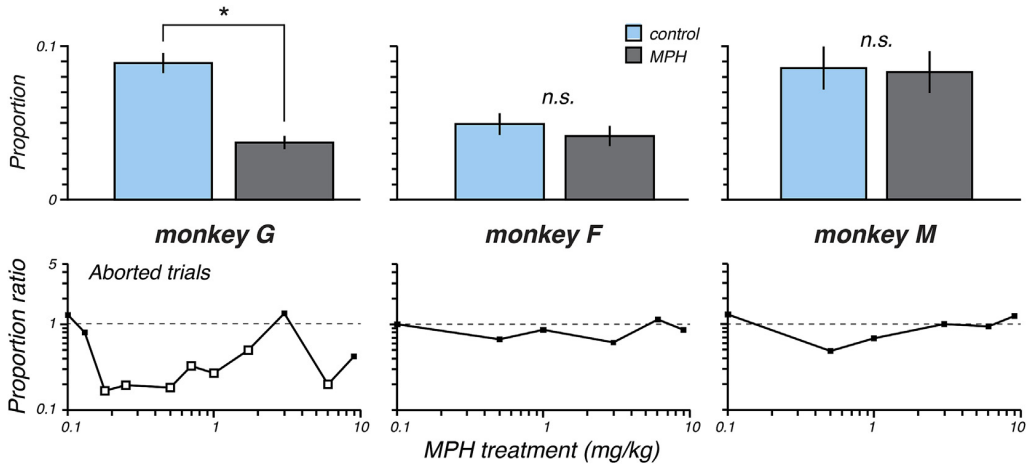

Fig. 6. MPH effects on task engagement: Aborted trials. *Top*: Proportion of aborted trials across all treatment and corresponding control sessions. Error bars, 95% confidence intervals. Asterisk, statistically significant difference (χ^2 test, $p < 0.05$). *Bottom*: Ratio between the proportions of aborted trials in treatment and corresponding control sessions as a function of MPH dose. Ratio <1 signifies improvement. Doses with significantly different proportions are indicated with large white squares.

treatment sessions than corresponding control sessions (rank sum tests, $p < 0.05$; 7 out 11 sessions for *monkey G*; 4 out 6 for *monkey F*). In contrast, this was the case in only one out of six sessions in *monkey M*. Nevertheless, the distribution of trial initiation times varied significantly with dose in each animal (Kruskal-Wallis, test, $p < 0.0001$). Fig. 7 (*middle*) shows the ratio between the mean trial initiation time observed in treatment and corresponding control sessions as a function of MPH dose. Complementary to this measure, we also computed the proportion of trials starting with the animal's gaze at the fixation point. The proportion of such already initiated trials was significantly higher in treatment sessions for both *monkey G* (0.58 vs. 0.50, χ^2 test, $p < 0.0001$, $\phi = 0.083$) and *monkey F* (0.31 vs. 0.27, $p < 0.0001$, $\phi = 0.049$), but lower for *monkey M* (0.16 vs. 0.18, $p = 0.0014$, $\phi = 0.038$). Within each monkey, this

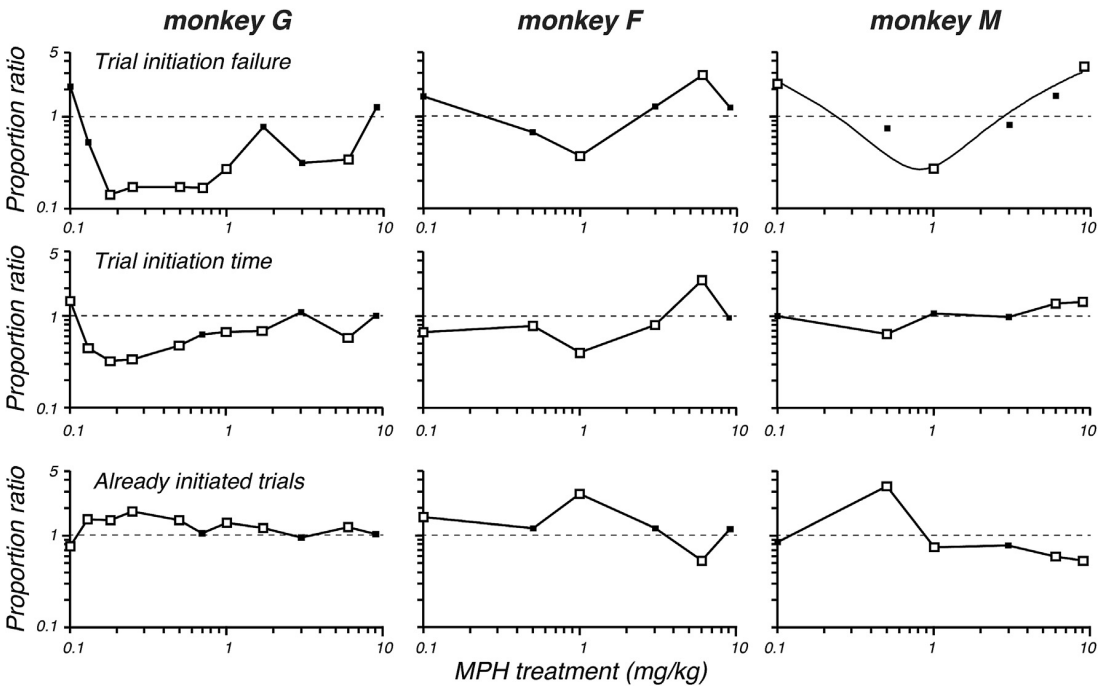

Fig. 7. MPH effects on task engagement: Fixation initiation. *Top*: Ratio between the proportions of trial initiation failures in treatment and corresponding control sessions as a function of MPH dose. Ratio <1 signifies improvement. *Middle*: Ratio between the mean trial initiation time observed in treatment and corresponding control sessions as a function of MPH dose. Ratio <1 signifies improvement. *Bottom*: Ratio between the proportions of already initiated trials (trials starting with the animal's gaze at the fixation point) in treatment and corresponding control sessions as a function of MPH dose. Ratio >1 signifies improvement. Doses with significantly different proportions are indicated with large white squares. Data points are connected with straight lines, with the exception of the top-right graph, in which a quadratic model fit was statistically significant ($y = 2.52x^2 + 0.42x + 0.27$; $R^2 = 0.91$, F test, $p = 0.029$).

proportion varied with dose (χ^2 test, $p < 0.0001$, $\phi = 0.11–0.19$). Fig. 7 (*bottom*) shows the ratio between the proportions of already initiated trials in treatment and corresponding control sessions as a function of MPH dose. Improvement (reflected with a ratio >1) was found to reach statistical significance in seven (out of twelve) treatment sessions in *monkey G* (repeated χ^2 test, sequentially rejective Holm-Bonferroni, $p < 0.05$), in two out of six in *monkey F*, and in one out of six in *monkey M*.

Lastly, we also noticed that *monkey M* performed particularly longer sessions following treatment. This observation is in line with that of Rajala et al. (2012), however, that measure largely depends on satiety, which itself depends on several non-experimental factors more difficult to control. Nevertheless, we computed the total number of trials performed by each animal and tested whether these were significantly larger in treatment versus corresponding control sessions. We found that this was indeed the case for *monkey M*, for which treatment sessions had 51% more trials on average (952 vs. 631; paired *t*-test, $p = 0.01$). The other two monkeys did not show any statistically significant difference in the number of trials performed in treatment and control sessions (*monkey F*: 1242 vs. 1062, $p = 0.16$; *monkey G*: 697 vs. 755, $p = 0.09$). Fig. 8 shows the ratio between the total number of trials performed in treatment and corresponding control sessions as a function of MPH dose. No strong dose-dependency can be detected.

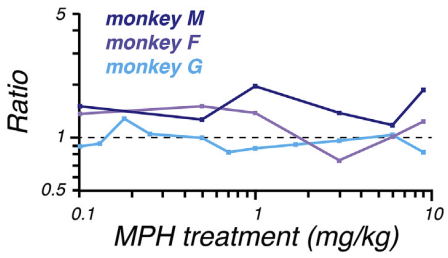

Fig. 8. MPH effects on task engagement: Numbers of trials. Ratio between the total number of trials performed in treatment and corresponding control sessions as a function of MPH dose. Ratio >1 signifies improvement.

In summary, results from different measures suggest that MPH enhanced task engagement in each animal, even though these measures did not necessarily covary. Following treatment, *monkey G* aborted significantly less trials and initiated significantly more trials and more quickly, *monkey F* initiated trials significantly more quickly, and *monkey M* performed significantly more trials. We also observed dose-dependent changes in all these measures, and significantly enhanced task engagement was thus observed for some specific doses. Nevertheless, these dose-dependent changes were generally irregular and the best quadratic fit was practically never statistically significant (F test, $p > 0.05$); the only exception was for the trial initiation failure data in *monkey M* (Fig. 7, *top right*). If there were best doses, these were within the lower end of the range we tested (0.18–1 mg/kg).

4. Discussion

Monkeys received a wide range of doses of the catecholamine reuptake inhibitor MPH before being tested on a visual sequential comparison task that measured their working memory ability. Neither a dose-dependent (e.g., inverted-U dose response curve) nor a memory load-dependent effect of MPH on response accuracy or latency was found. In contrast, MPH had a beneficial effect on task engagement in all monkeys, although different measures were

affected in different animals. The results obtained suggest that MPH does not affect the retention of visual information in working memory directly. These findings are at odds with our predictions, considering the pharmacological characteristics of MPH and its implications in the treatment of attention deficit hyperactivity disorder (ADHD). However, closer inspection of previous studies suggests that the results are not entirely inconsistent with reported effects of MPH and that putative inconsistencies can be reconciled.

Early non-human primate studies that have investigated the effects of MPH, have reported no (Bartus, 1978) or detrimental effects (Bartus, 1979) on working memory ability, especially in aged animals. Conversely, more recent studies have reported enhancing effects of MPH on delayed response (Gamo et al., 2010; Rajala et al., 2012) and DMTS performance (Bain et al., 2003; but see Soto et al., 2013 as well as Hutsell and Banks, 2015). However, best-dose analyses—as used in Gamo et al. (2010)—are prone to false positives (Soto et al., 2013). Moreover, in the other two studies, MPH seemed to mainly affect distractibility (Bain et al., 2003) or premature responding (Rajala et al., 2012) rather than working memory per se. Rajala et al. (2012) reported a dose-dependent increase in the amount of time monkeys engaged in the task. Schneider et al. (1994) reported that DA-depleted (MPTP-treated) monkeys seemed more focused while performing a delayed response task after MPH treatment, which decreased the occurrence of omissions, without a significant effect on errors.

Overall, MPH may exert its effects by enhancing task engagement. According to the adaptive gain theory (Aston-Jones and Cohen, 2005), task engagement (the balance between exploration and exploitation behavior) is regulated by the pattern of NE release by locus coeruleus (LC) neurons, thought to be regulated by task utility evaluated by frontal areas. Increasing utility could therefore lead to greater engagement via an increase in bursting activity from LC neurons. A growing body of work suggests that motivation/reinforcement may overcome the cost inherent to the exertion of cognitive control (see for review Botvinick and Braver, 2015). At the very least, task engagement is a prerequisite for cognitive processing, and MPH could enhance task engagement through its effect on NE or DA systems, or both. For instance, Marquand et al. (2011) reported that some MPH effects on brain activation in non-rewarded trials of a delayed match-to-position task was similar to that observed in rewarded trials. In addition, Volkow et al. (2004) reported MPH-induced increases in striatal DA that correlate with self-reports about how a mathematical task was interesting, exciting and motivating. Interestingly, models of ADHD include motivational deficits, which are characterized by delay aversion (Sonuga-Barke, 2003; Sonuga-Barke et al., 2010) as well as impaired reward sensitivity (Tripp and Wickens, 2008; Luman et al., 2010), and it has been shown that abnormal reward motivation can be normalized by MPH (Aarts et al., 2015).

Neuroimaging evidence suggests that MPH modulates cognition by enhancing the activation of the fronto-parietal network and deactivation of the default mode network (DMN) (Marquand et al., 2011; Tomasi et al., 2011). In ADHD, the DMN is inadequately attenuated during task engagement, which could interfere with cognitive processes required for goal-directed behavior (Sonuga-Barke and Castellanos, 2007; Cortese et al., 2012). Accordingly, MPH administration normalizes the pattern of task-related DMN deactivation in children with ADHD, rendering it indistinguishable from that of typically developing children during an inhibitory control task (Liddle et al., 2011). Enhanced connectivity within motivation/reinforcement regions and their decreased connectivity with default-mode regions suggests impaired interactions between control and reward pathways in ADHD, which may underlie attention and motivation deficits in ADHD (Tomasi and Volkow, 2012).

In this study, MPH was expected to alter working memory largely because of its application in ADHD treatment, where it has been widely shown to improve this cognitive ability in children and adults (Martinussen et al., 2005; Nigg, 2005; Willcutt et al., 2005; Pietrzak et al., 2006; Kasper et al., 2012; Coghill et al., 2014). Nevertheless, it is unclear whether ADHD patients are responsive to MPH because of higher DA transporter density (see for review Fusar-Poli et al., 2012); no significant change in NE transporter density have been found (Vanicek et al., 2014). To the best of our knowledge, the monkeys in this study have unimpaired catecholamine systems, but understanding the effects of MPH in healthy subjects is an important step, as stimulants are increasingly being used recreationally as putative cognitive enhancers (McCabe et al., 2005, 2014; Smith and Farah, 2011; Ilieva et al., 2015). Thus far, evidence for MPH enhancing working memory in the healthy brain is limited, and that its effects on cognition seem modest at most (see for review Ilieva et al., 2015). Our findings that MPH has some beneficial effects on task engagement is consistent with the report from Ilieva and Farah (2013), who suggested that the stimulant-induced enhancement perceived by healthy users has a significant motivational component.

Our findings suggest that MPH does not alter working memory ability in healthy, well-trained individuals. Monkey studies using delayed response tasks have shown that DA depletion (Brozoski et al., 1979) and administration of DRD1 antagonists (Sawaguchi and Goldman-Rakic, 1991, 1994) in prefrontal cortex can lead to pronounced impairments in working memory ability. In aged monkeys, with a natural decline in catecholamine concentrations (Goldman-Rakic and Brown, 1981; Wang et al., 1998), DRD1 agonists have been reported to enhance working memory (Arnsten et al., 1994; Cai and Arnsten, 1997); the evidence is more equivocal for young adults (Arnsten et al., 1994; see also Dudkin et al., 2003; Castner and Goldman-Rakic, 2004). NRα2 agonists have been reported to increase performance and reduce distractibility in aged and catecholamine-depleted (Arnsten and Goldman-Rakic, 1985; Arnsten et al., 1988; Cai et al., 1993; O'Neill et al., 2000; Decamp et al., 2011), but not in adult control monkeys (Arnsten and Goldman-Rakic, 1985). Conversely, some studies reported improved performance in adult monkeys with NRα2 agonists; however, at high, but not low or intermediate doses (Franowicz and Arnsten, 1998, 1999). At the high doses required for this effect, NE could have activated not only the NRα2, but also lower affinity α1- and β1-receptors, which have been suggested to play opposing roles in working memory (Arnsten and Jentsch, 1997; Ramos et al., 2005). Altogether, it seems that increased levels of DA or NE with unimpaired catecholamine systems produce only minimal effects on working memory. Worthy of note, the above studies assessed working memory using a single memorandum and delayed response tasks with long retention intervals, which could provide sufficient time for long-term memory representations to be formed and affect performance. The human literature has similarly produced inconsistent results regarding the effects of DA and NE on working memory in healthy individuals. Overall, there is limited evidence that performance in a variety of working memory tasks is reliably modulated by catecholamine depletion (Harmer et al., 2001; Harrison et al., 2004; McLean et al., 2004; Ellis et al., 2005; Mehta et al., 2005; Linssen et al., 2011), DA receptor agonists (Luciana et al., 1992, 1998; Kimberg et al., 1997; Luciana and Collins, 1997; Müller et al., 1998; Mehta et al., 2001; Bartholomeusz et al., 2003; Kimberg and D'Esposito, 2003; Gibbs and D'Esposito, 2005; see for review Cools and D'Esposito, 2011) or NE receptor agonist (Frith et al., 1985; Coull et al., 1995; Jäkälä et al., 1999a, 1999b; Middleton et al., 1999; Müller et al., 2005; Tiplady et al., 2005; Swartz et al., 2008; McAllister et al., 2011; see for review Chamberlain and Robbins, 2013).

Traditionally, MPH has been thought to act in an 'inverted-U' dose-dependent manner, whereby optimal doses lead to maximal enhancement of cognitive abilities, such as working memory, and lower or higher doses have no or detrimental effects on such abilities (e.g., Berridge et al., 2006; Levy, 2009; Gamo et al., 2010). It could be argued that no enhancing effects of MPH on working memory accuracy were observed in this study, because the effectiveness of DA and NE was already sufficient, thus suggesting levels at the peak of a theoretical 'inverted-U' curve. If that were the case, however, we would have expected to see detrimental effects of MPH on working memory as it pushes DA and NE levels onto the descending slope of the curve. The starting point on such a curve is unknown, however, since we observed no obviously pattern of detrimental or enhancing effects over a wide range of MPH doses, we must conclude that the effects of MPH on working memory per se does not follow an 'inverted-U' dose pattern. Furthermore, the beneficial effects on motivational measures that we observed were within the lower end of the range of doses that we tested. In addition, these dose-dependent effects only very loosely followed a 'U' or 'inverted-U' function; best fits with quadratic models in all but one data set were not statistically significant.

As dose-dependent effect of MPH on response accuracy was not observed, we investigated response latency as a second measure of performance. Without affecting response accuracy, MPH could have improved processing, which could have been reflected in shorter response latencies. Few studies investigating MPH's effect on working memory reported effects on response latency, and those that have report inconsistent results. In monkeys, Bain et al. (2003) reported a decrease in response latency for the individually determined best dose; whether this effect was dose-dependent is unclear. In rats, no effect on response latency has been observed (Arnsten and Dudley, 2005; Berridge et al., 2006). Similarly, in ADHD patients, no effect was observed (Rhodes et al., 2004), while in healthy humans shorter response latencies have been reported with MPH (Tomasi et al., 2011). Overall, it remains unclear whether MPH affects the latency of behavioral responses.

5. Conclusion

MPH did not affect response accuracy or latency in the predicted dose- or memory load-dependent way. By implementing a working memory task designed to minimize the influence of other cognitive functions on performance, these findings suggest that MPH does not affect working memory ability per se. In contrast, various measures of task engagement were positively affected by the administration of MPH. It thus remains controversial whether putative cognitive enhancers, including MPH, directly improve cognitive functions, such as working memory, or whether they affect motivation and potentially reward sensitivity instead. Despite the lack of effects of task performance observed on this study, MPH in doses tested here could have an impact on neural activity and on other behavioral measures. This possibility needs to be investigated in future studies.

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