Catecholaminergic modulation of the avoidance of cognitive control

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SUPPLEMENT

I. Supplemental Methods

Supplemental methods 1*: Need for Cognition Scale*

The self-report Need for Cognition Scale (Cacioppo & Petty, 1982; Cacioppo, Petty, & Kao, 1984) was administered to investigate participants' tendency (trait) to engage in effortful tasks. The scale consists of 18 statements, which participants rate on a 5-point Likert scale ("extremely uncharacteristic of me" to "extremely characteristic of me"). Example statements include "I prefer complex to simple problems" or "I only think as hard as I have to". Scores range from 18 to 90. Results of the relation between participants' need for cognition scores and their degree of demand avoidance are presented in the supplemental results (see Supplemental Results 4). In this study, we did not have specific hypotheses for this scale, but aimed to relate to existing work by reporting whether demand avoidance as quantified with the demand selection task relates to this measure. Thus, we correlated the proportion of low-demand choices (i.e. demand avoidance) to participants' scores on the Need for Cognition scale using IBM SPSS for Windows, version 21 (IBM Corp., Armonk, N.Y., USA).

Supplemental methods 2: *Statistical analyses – additional control analyses*

We performed a number of control analyses using a model comparison approach, where we assessed whether the residual sum of squares was reduced when adding any of the following factors: order effects of drug and testing day, gender, and NLV scores (as a measure of verbal intelligence). Results of these control analyses are presented in Supplemental Results 5 and Supplemental Table 6.

To assess whether our key MPH effects of interest can be accounted for by nonspecific effects of MPH on mood and medical symptoms, we extracted subjective ratings of the PANAS scale (Watson, Clark, & Tellegen, 1988), Bond and Lader Visual Analogue Scale (Bond & Lader, 1974) and the medical analogue scale (Supplemental Material 2) and performed a repeated measures MANOVA with the within-subject factors Time (3: start of testing day, before task battery, after task battery) and Drug (2: MPH, placebo) and the six measures as dependent variables (positive affect, negative affect, calmness, alertness, contentedness, medical symptoms) using IBM SPSS for Windows, version 21 (IBM Corp., Armonk, N.Y., USA). Significant effects were followed up with repeated measure ANOVA. Results are presented in Supplemental Results 5.

Supplemental Material 1: *Overview of exclusion criteria*

- (History of) psychiatric treatment
- (History of) neurological treatment
- (History of) endocrine treatment
- (History of) autonomic failure (e.g., vasovagal reflex syncope).
- (History of) clinically significant hepatic, cardiac, obstructive respiratory, renal, cerebrovascular, metabolic or pulmonary disease
- Family history of sudden death or ventricular arrhythmia
- (History of) epilepsy
- (History of) drug dependence (opiate, LSD, (meth)amphetamine, cocaine, solvents, or barbiturate) or alcohol dependence
- Suicidality
- Abnormal hearing or (uncorrected) vision.
- Use of MAO inhibitor, anaesthetic, anti-depressant or antipsychotic drugs within the week prior to the start of the study.
- Use of psychotropic medication, or of recreational drugs over a period of 24 hours prior to each test session, and use of alcohol within the last 24 hours before each measurement.
- Regular use of corticosteroids.
- Uncontrolled hypertension, defined as diastolic blood pressure at rest > 95 mmHg or systolic blood pressure at rest > 180 mmHg
- Hypotension, defined as diastolic blood pressure < 50 mm Hg or systolic < 95 mm Hg or resting pulse rate < 45 beats/min
- Diabetes
- Family history of schizophrenia, bipolar disorder or major depressive disorder
- Irregular sleep/wake rhythm (e.g., regular nightshifts or cross timeline travel).
- Possible pregnancy or breastfeeding
- Lactose intolerance (placebo pill is a lactose product)

***Supplemental Material 2*:** *Medical symptoms rating scale*

1. No headache	Strong headache
2. No muscle pain	Strong muscle pain
3. No dry mouth	Very dry mouth
4. Not dizzy	Very dizzy
5. No abdominal pain	Strong abdominal pain
6. No joint pain	Strong joint pain
7. No trouble breathing	Trouble breathing
8. No throat pain	Strong throat pain
9. No chest pain	Strong chest pain
10. No eye problems	Strong eye problems

II. Supplemental Results

Supplemental Results 1*: Effects of MPH as a function of working memory capacity*

Listening span scores varied from 2.5 to 7 with a median of 4.5. This median and range is comparable with values observed in previous studies including young populations (Salthouse & Babcock, 1991). The listening span-dependent effects of MPH, described in the main text, are shown in Supplemental Figures 4A and 4B.

Supplementary analysis after exclusion of participants who failed to explore at all, who switched cues on every trial, for whom the capsule dissolved early as well as an outlier on trait impulsivity scores also did not reveal any significant MPH-effects as a function of working-memory capacity (n = 74: Drug x Listening span: $X^2(1) = 0.68$, $p = 0.408$).

MPH did alter the reaction time demand cost as a function of listening span (Drug x Listening span x Demand: $X^2(1) = 4.11$, $p = 0.043$; Supplemental Figure 5A). High-span participants exhibited MPH-induced decreases in the RT demand cost, whereas low-span participants exhibited MPH-induced increases in the RT demand cost. However, note that in a model that takes into account response stickiness (see Supplemental Results 2 and Supplemental Table 5), this interaction did not reach significance (Drug x Listening span x Demand: $X^2(1) = 3.63$, $p = 0.057$). There was no span-dependent effect on the error demand cost: Drug x Listening span x Demand: $X^2(1) = 0.20$, $p = 0.657$, Supplemental Figure 5B).

In sum, relative to low working memory-span participants, high-span participants (tend to) exhibit MPH-induced improvement in task switching (in terms of RT demand costs), but MPH did not affect demand avoidance robustly as a function of working memory. We are puzzled by the lack of an effect of WM capacity, particularly given the effect of trait impulsivity, which has also been associated with dopamine transmission. We raise two alternative accounts of this pattern, although we also note that we do not provide evidence for a significantly greater impact of impulsivity than of WM capacity. First, trait impulsivity might be a more reliable proxy of baseline dopamine levels than WM capacity. We would argue this is unlikely, particularly given the subjective, self-report nature of the former and not the latter proxy variable. Second, trait impulsivity might index a distinct aspect of dopamine transmission (striatal dopamine release; Buckholtz et al., 2010; Dalley et al., 2007) that might be more determinant of the effect of MPH on demand avoidance than the dimension captured by WM capacity (striatal and probably prefrontal dopamine synthesis capacity).

Our hypothesis regarding WM span was bi-directional. The finding of beneficial MPH-effects in high-span participants contrasts with prior evidence, showing greater potentiation by MPH of performance on working memory and sustained attention tasks in low- than high-span participants (Del Campo et al., 2013; Mehta et al., 2000). However, on hindsight, the positive correlation between WM span and MPH effects is not surprising, given that, as is the case for impulsivity (Buckholtz et al., 2010), WM span is also associated with higher striatal dopamine function. Moreover, our effect generally concurs with other evidence, indicating, conversely, greater potentiation by MPH of learning in high- than low-capacity subjects (van der Schaaf, Fallon, Ter Huurne, Buitelaar, & Cools, 2013) as well as greater MPH-induced increases in dopamine release in higher-performing participants (Del Campo et al., 2013). Finally, it fits with the dopamine cell-activity hypothesis (Volkow et al., 2002) suggesting that DAT blockade (with MPH) induces larger dopamine increases in subjects with high relative to low dopamine cell activity. We remain puzzled by these discrepant effects of working memory span across studies, but speculate that they reflect catecholaminergic modulation of different neural regions with distinct optimal levels of dopamine (e.g. Fallon and Cools, 2015). For example, the enhancing effects of MPH on learning and task switching might reflect catecholaminergic modulation of the striatum, whereas the impairing effects of MPH on working memory and sustained attention, reported previously, might reflect modulation of the prefrontal cortex, consistent with the disproportionate vulnerability of the prefrontal cortex to supra-optimal dopamine (D1) receptor stimulation (Berridge & Arnsten, 2015; Seamans & Yang, 2004; Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007; Williams & Goldman-Rakic, 1995). Clearly this speculative hypothesis should be tested using pharmacological fMRI.

Supplemental Results 2*: Performance models including stay regressor*

For the purpose of consistency with our approach for the choice analyses, we re-ran the performance models (accuracy and response times), when including the response stickiness regressor as main effect and interacting effect with MPH (and demand). We then did model comparisons using the anova function in R to assess whether the reduction in the residual sum of squares is statistically significant compared with the simpler models. For accuracy, a model without any stickiness regressor shows the smallest BIC (31220). Adding a stickiness regressor did not reduce residual sum of squares significantly (versus main effect of stickiness: X^2 (6) = 3.6, p = 0.733; versus interactive effect of stickiness: X^2 (30) = 21.5, p = 0.872). For response times, however, the model with the lowest BIC that shows a significant reduction of residual sum of squares compared with the other two models, is a model that includes stickiness as interactive term (BIC = 137710, versus basic model: X^2 (30) = 2575.3, p < 0.001); versus stickiness main effect: X^2 (24) = 2113.5, p < 0.001). Results of this winning model are presented in Supplemental Table 5.

Supplemental Results 3*: Performance models including task-switching*

Participants' choices of low versus high demand options determine the degree of task-switching that they encounter and therefore also the 'practice' of one or the other trial type. To quantify this effect, we re-ran performance models (Supplemental Table 1, bottom), but now including the factor task-switching as predictor in addition to demand. The model confirms that switch-costs are larger on low demand trials relative to high demand trials. This only holds for response times (task-switch x demand interaction: X^2(1) = 372.7, p <

0.001), and not for accuracy (task-switch x demand interaction: $X^2(1) = 0.4$, p = 0.547. Critically, this interaction in response times was not modulated by MPH (Drug x task-switch x demand: $X^2(1) = 1.8$, p = 0.179), also not as a function of impulsivity scores (Drug x task-switch x demand x Impulsivity: $X^2(1) = 1.2$, p = 0.266).

Supplemental Results 4*: Need for Cognition Scale and demand avoidance*

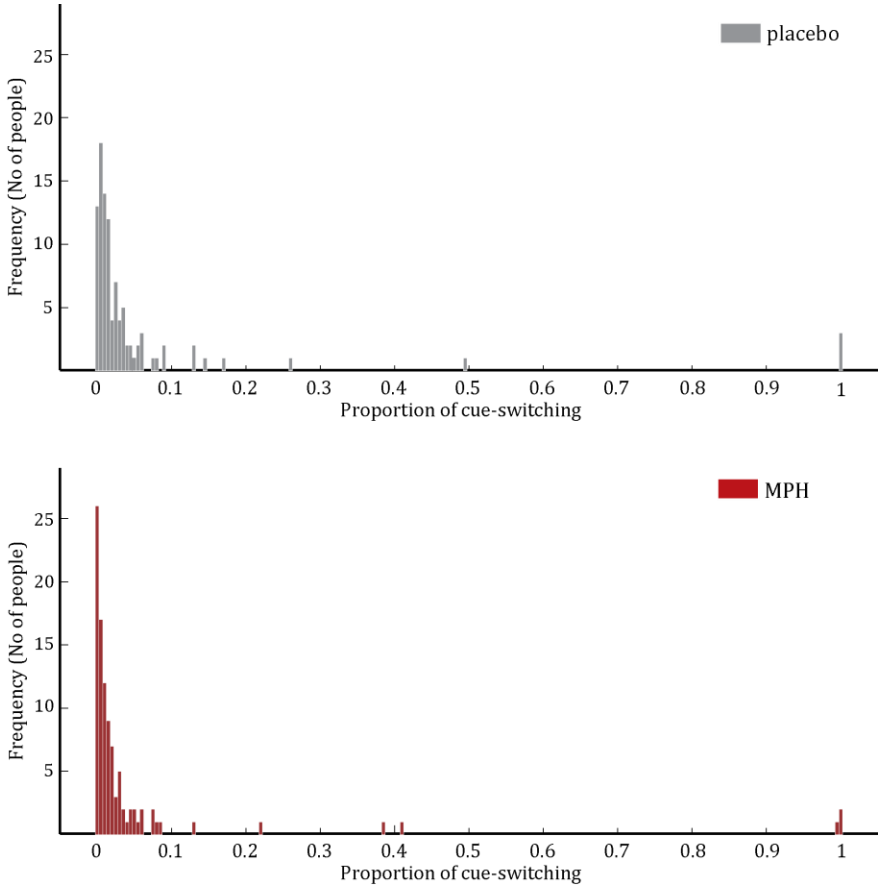
Participants' average score on the Need for Cognition (NFC) scale was 63.3 (*SD* = 10.5) ranging from 38 to 82. These values are comparable with those reported previously (e.g. Westbrook et al., 2013). The Need for Cognition score did not correlate with the degree of demand avoidance in the placebo (NFC & low demand choices: $r = 0.13$, $p = 0.212$), in the MPH session (NFC & low demand choices: $r = -0.07$, $p = 0.498$) or with the effect of MPH relative to placebo on demand avoidance (NFC & low demand choices $_{MPH - PLA}$: $r = -0.15$, $p = 0.133$).

Supplemental Results 5*: Additional control analyses*

We performed model comparisons with models including potentially confounding variables of no interest. We included the factors order of intervention, testing day, gender, and verbal intelligence (NLV) separately as fixed between-subject factors in the basic models, resulting in 12 comparisons presented in Supplemental Table 6. Models including order, day, gender or NLV did not explain more variance than the basic models, except for adding the factor day to the response time model. Including day (*BIC* = 139860) explained significantly more variance than the basic model (*BIC* = 139935; $X^2(1) = 86.60$, p < 0.001). However, significance and interpretation of reported effects were not altered in a model including day.

The administration of MPH altered participants' mood ratings (positive affect, negative affect, alertness, contentedness, calmness) and medical symptoms (Supplemental Material 2) significantly (MANOVA: Drug x Time [3]: $V = 0.28$, $F(6,12) = 5.30$, $p < 0.001$) in the absence of differences at time zero before drug administration (Drug: V = 0.06, F(6, 93) = 0.91, p = 0.492). MPH increased subjective report of positive affect ($F(1,98) = 18.26$, $p < 0.001$), alertness ($F(1,98) = 16.88$, $p < 0.001$), medical symptoms ($F(1,98) = 9.60$, $p = 0.003$) and decreased calmness ($F(1,98) = 8.65$, $p = 0.004$), all with respect to baseline (Drug x Time, measurement 1 versus later). To explore whether these mood and medical measures differed between dug sessions at the time point most proximal to the demand selection task, we conducted the same analysis again for the second time point and assessed whether this interacts with impulsivity scores. Results of this repeated measures MANOVA reveal no significant modulation across all measures in multivariate (Drug x Impulsivity: $F(6,93) = 1.31$, $p = 0.260$) nor for each measure in univariate tests. In addition, when correlating drug-induced changes on all six mood and medical measures at this same time point with drug-induced changes in demand avoidance, none of these correlations reached significance (all p-values > 0.2). In sum, it is unlikely that MPH-induced mood or medical changes underlie our effect of interest: an impulsivity-dependent modulation of demand avoidance.

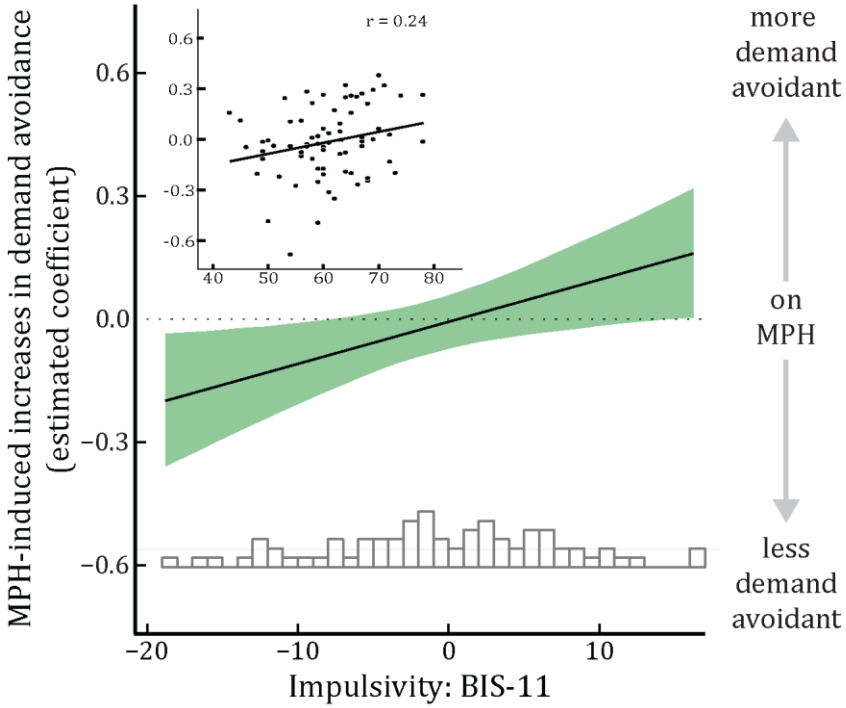
Supplemental Figure 1 - Histogram of the proportion of participant's response switches between the two choice options as a function of drug. A high frequency of participants showed low exploration of the two choice options. Choices of 3 participants deviated more than 3 standard deviations from the group's mean regarding their extreme exploration behavior on placebo and methylphenidate sessions (proportion switching above 0.99).



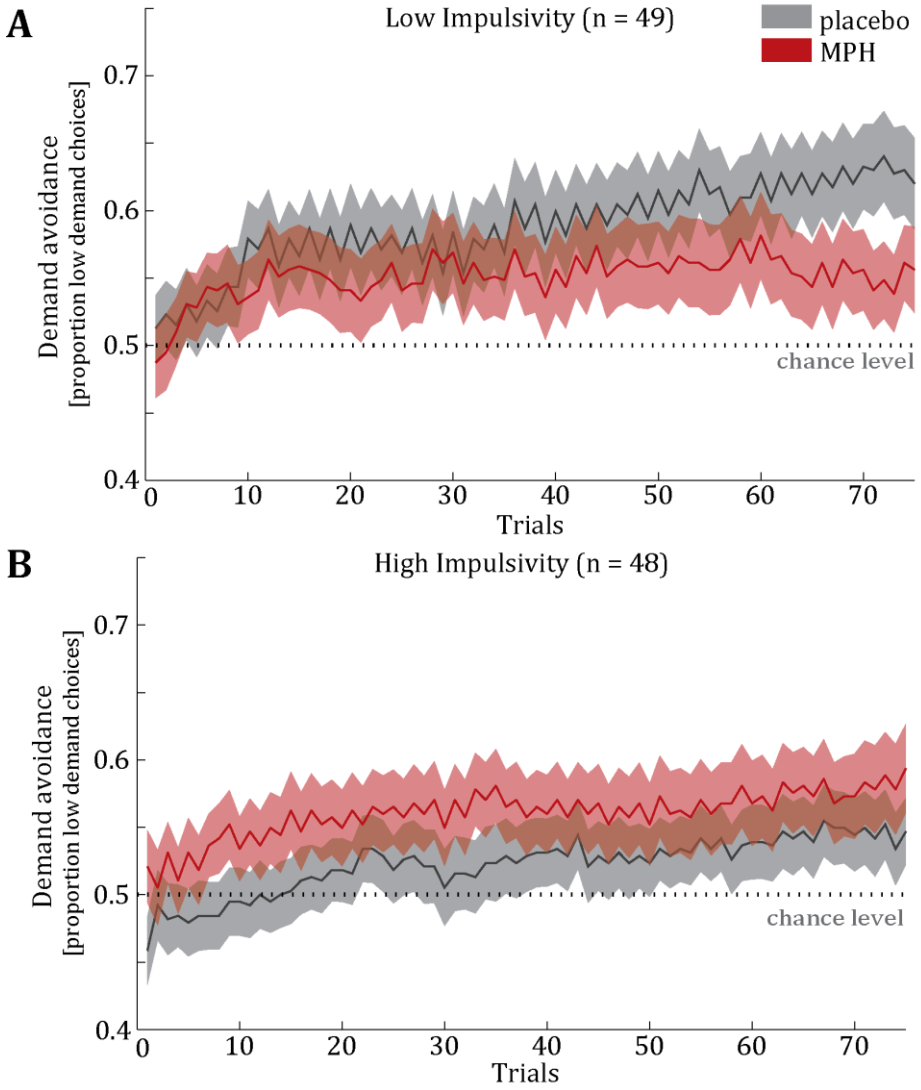
Note that this low rate of exploration would have resulted in extremely skewed distribution of our dependent variable of interest, i.e. demand avoidance. However, by making use of 8 different task blocks where low and high demand options appear at different locations and have different visual identities, the key variable of demand avoidance is not significantly skewed. The distribution of the variable of interest, the proportion of low demand choices, is depicted in Figure 2B.

Supplemental Figure 2 –Methylphenidate-effect on demand avoidance as a function of participants' trait impulsivity (BIS-11) scores for the reduced sample (n = 74). Line

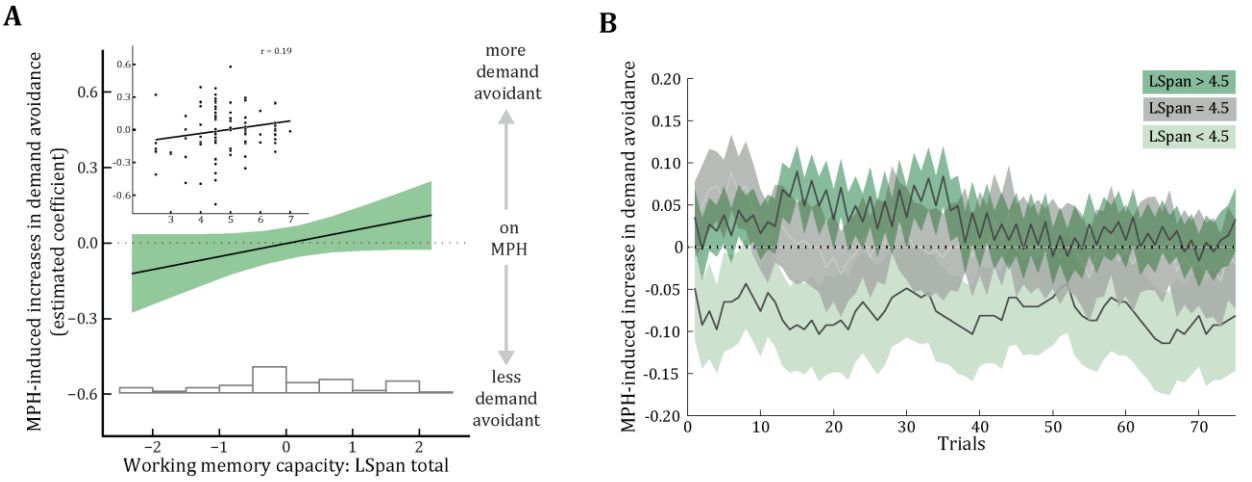
represents model-based estimated coefficients of MPH-effect on demand avoidance as a function of (z-scored) trait impulsivity scores. Shaded area represents simulated 95% confidential intervals of the coefficients. The inset shows the raw data: drug effect for every participant (n = 74) across trials as the difference in the proportion of low demand choices (MPH - placebo) as a function of trait impulsivity.



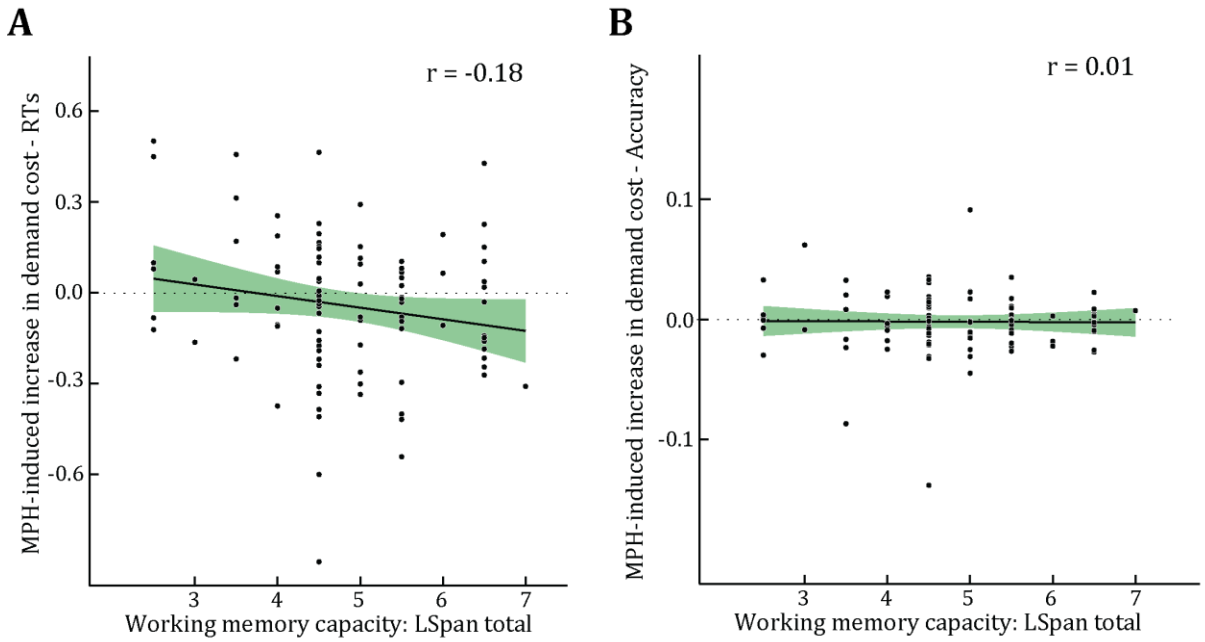
Supplemental Figure 3- Methylphenidate-effect on demand avoidance varied as a function of participants' trait impulsivity. Data points represent proportion of low demand choices averaged across participants (n = 100) across 8 blocks for **A** low and **B** high impulsive participants as a function of trial. Three participants with median scores are not included in this plot.



Supplemental Figure 4 – Methylphenidate (MPH)-effect on demand avoidance as a function of participants' working memory capacity does not reach statistical significance. Data points represent effects of MPH, relative to placebo, on the proportion of low demand choices (MPH minus placebo). **A** Line represents model-based estimated coefficients of MPH-effect on demand avoidance as a function of (z-scored) listening span total scores. Shaded area represents simulated 95% confidential intervals of the coefficients. The inset shows the raw data: drug effect for every participant (n = 100) across trials as the difference in the proportion of low demand choices (MPH - placebo) as a function of listening span scores. **B** Trial-by-trial drug effect averaged across 8 blocks, and across participants (n = 100) of low (n = 23), medium (n = 31) and high (n = 46) listening span groups as a function of trial. Shaded areas represent standard error of the difference.



Supplemental Figure 5 - Drug effects on demand cost in response times (RTs) and accuracy. Data points represent methylphenidate (MPH)-effects on average demand cost (MPH minus placebo) for each participant for **A** response times as a function of working memory capacity (listening span total, significant, p = 0.043) and **B** accuracy as a function of working memory capacity (listening span total, not significant, p = 0.657). Shaded areas represent standard errors of the difference.



***Supplemental Table 1*:** *Overview of regression models*

Dependent variable	Regression models
Choice category: binary	Choice ~ Drug x Impulsivity + Drug x Listening span + (1 + Drug | Participant)
Choice with stay regressor	Choice ~ Drug x Impulsivity + Drug x Listening span + Stay + (1 + Drug + Stay | Participant)
Choice with MPH-effect on stay regressor	Choice ~ Drug x Impulsivity + Drug x Listening span + Drug x Stay + (1 + Drug x Stay | Participant)
Accuracy category: binary	Accuracy ~ Drug x Impulsivity x Demand + Drug x Listening span x Demand + (1 + Drug x Demand | Participant)
Response times category: continuous	RT ~ Drug x Impulsivity x Demand + Drug x Listening span x Demand + (1 + Drug x Demand | Participant)

Supplemental Table 2: Logistic regression coefficients indicating the influence of drug, impulsivity, listening span, choice on previous trial (staying) and their interactions with drug on participants' choices (n = 100). Bold p-values denote significance. For this model, the marginal R^2_{GLMM} is 0.639.

Coefficient	Estimate (SE)	$X^2(1)$	*p*
Intercept	*-0.184 (0.04)*	*20.70*	***< 0.001***
Drug	*-0.001 (0.03)*	*< 0.01*	*0.964*
Drug x Impulsivity	*0.009 (<0.01)*	*5.33*	***0.021***
Drug x Listening span	*0.052 (0.03)*	*2.91*	*0.088*
Impulsivity	*-0.001 (0.01)*	*0.07*	*0.793*
Listening span	*-0.029 (0.04)*	*0.57*	*0.451*
Staying	*-4.239 (0.25)*	*291.16*	***< 0.001***
Drug x Staying	*0.238 (0.09)*	*7.65*	***0.006***

Supplemental Table 3: Performance and choice statistics of effects of interest after the exclusion of participants who failed to explore the choice options at all, either in one (n = 17) or both session (n = 5), those who switched choice options on every cue in one (n =1) or both (n = 1) sessions , those for whom the capsule dissolved (orally or in water) before swallowing (n = 2, one of those was also a sticky participant) as well as one participant whose score on the BIS-11 impulsiveness questionnaire deviated more than 3 standard deviations from the mean. Analysis of this smaller dataset (n = 74) confirmed the effects obtained from the analysis of the larger sample. Marginal R^2_{GLMM} of the choice, accuracy and response times models are 0.698, 0.013 and 0.090, respectively.

	Choice		**Accuracy**		**Response times**	
Coefficient	**$X^2(1)$**	***p***	**$X^2(1)$**	***p***	**$X^2(1)$**	***p***
Drug	*0.03*	*0.867*	*5.91*	***0.015***	*1.85*	*0.173*
Drug x Imp	*5.80*	***0.016***	*0.02*	*0.876*	*8.87*	***0.003***
Drug x LSpan	*0.68*	*0.408*	*0.69*	*0.408*	*1.92*	*0.165*
Drug x Demand	*N/A*	*N/A*	*1.46*	*0.228*	*0.31*	*0.580*
Drug x Imp x Demand	*N/A*	*N/A*	*1.01*	*0.315*	*0.10*	*0.754*
Drug x LSpan x Demand	*N/A*	*N/A*	*0.17*	*0.679*	*0.64*	*0.425*
Stay	*465.64*	***< 0.001***	*N/A*	*N/A*	*N/A*	*N/A*
Drug x Stay	*4.80*	***0.029***	*N/A*	*N/A*	*N/A*	*N/A*

***Supplemental Table 4*:** (Logistic) regression coefficients indicating the influence of drug, impulsivity (Imp), listening span (LSpan), task demand and their interactions on participants' performance (n = 100). Bold p-values denote significance. Marginal R^2_{GLMM} of the accuracy and response times models are 0.011 and 0.086, respectively.

	Accuracy			**Response times**		
Coefficient	**Estimate (SE)**	**$X^2(1)$**	***p***	**Estimate (SE)**	**$X^2(1)$**	***p***
Intercept	*3.868 (0.10)*	*1469.47*	***< 0.001***	*-0.123 (0.02)*	*45.22*	***< 0.001***
Drug	*-0.112 (0.04)*	*7.29*	***0.007***	*0.016 (0.01)*	*2.98*	*0.084*
Drug x Imp	*0.001 (0.01)*	*0.10*	*0.747*	*0.003 (<0.01)*	*7.28*	***0.007***
Drug x LSpan	*0.012 (0.04)*	*0.10*	*0.748*	*0.012 (0.01)*	*1.92*	*0.166*
Imp	*0.015 (0.01)*	*1.57*	*0.211*	*0.002 (<0.01)*	*1.12*	*0.289*
LSpan	*-0.045 (0.09)*	*0.23*	*0.635*	*-0.024 (0.02)*	*1.95*	*0.163*
Demand	*0.106 (0.03)*	*15.50*	***< 0.001***	*-0.139 (0.01)*	*535.73*	***< 0.001***
Drug x Demand	*-0.027 (0.02)*	*1.20*	*0.274*	*-0.003 (<0.01)*	*0.75*	*0.387*
Drug x Imp x Demand	*<0.001 (<0.01)*	*<0.01*	*0.968*	*-0.000 (<0.01)*	*0.29*	*0.590*
Drug x LSpan x Demand	*-0.008 (0.02)*	*0.20*	*0.657*	*-0.007 (<0.01)*	*4.11*	***0.043***

Supplemental Table 5: *Regression coefficients indicating the influence of drug, impulsivity (Imp), listening span (LSpan), task demand, choice on previous trial (Stay) and their interactions on participants' response times (n = 100). Bold p-values denote deviations in significance relative to the basic RT model that did not account for response stickiness. Note that conclusions presented in the main text are unaltered.*

	Response times		
Coefficient	**Estimate (SE)**	**$X^2(1)$**	***p***
Intercept	*0.08 (0.02)*	*10.60*	*<0.001*
Drug	*0.004 (0.01)*	*0.15*	***0.700***
Drug x Imp	*0.003 (<0.01)*	*7.96*	*0.005*
Drug x LSpan	*0.012 (0.01)*	*2.05*	*0.152*
Imp	*0.002 (<0.01)*	*1.16*	*0.281*
LSpan	*-0.018 (0.02)*	*1.11*	*0.293*
Demand	*-0.076 (<0.01)*	*152.39*	*< 0.001*
Drug x Demand	*-0.002 (0.01)*	*0.17*	*0.681*
Drug x Imp x Demand	*-0.000 (<0.01)*	*0.36*	*0.548*
Drug x LSpan x Demand	*-0.006 (<0.01)*	*3.63*	***0.057***
Stay	*-0.070 (0.01)*	*173.84*	***<0.001***
Drug x Stay	*-0.002 (0.01)*	*0.16*	***0.687***
Drug x Demand x Stay	*0.011 (0.01)*	*2.38*	***0.123***

***Supplemental Table 6*:** Model comparison of basic models with control models. Bold p-values denote significance.

		Basic	**+ NLV**	**+ Day**	**+ Order**	**+ Gender**
Choice	BIC	150826	150838	150835	150837	150835
	sign.		p = 0.501	p = 0.079	p = 0.464	p = 0.105
Accuracy	BIC	31220	31232	31231	31232	31232
	sign.		p = 0.695	p = 0.509	p = 0.931	p = 0.924
Response times	BIC	139935	139946	**139860**	139946	139947
	sign.		p < 0.364	**p < 0.001**	p = 0.436	p = 0.806

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