Memory enhancement with stimulants: differential neural effects of methylphenidate, modafinil and caffeine

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Supplementary Material

Control analyses

We estimated the individual drug dose based on body weight (mg/kg). The data revealed no significant dose-performance relationships (all $p > .16$).

Drug order and learning effects

To identify drug order and learning effects, two repeated-measures ANOVAs were performed. First, an ANOVA with treatment (drug/ placebo) as within-subject factor and drug type (MPH/ MOD/ CAF) and drug order (first drug/ first placebo) as the between-subject factors was performed. This analysis showed no significant interaction with drug order * treatment nor with drug order * treatment * drug type (all $p > .22$). A second repeated-measures ANOVA with testing day (performance on day 1/ day 2) as within-subject factor and drug order and drug type as between-subject factors was performed. Likewise, there was no significant variance explained for day order nor for day order * drug type, day order * drug order or day order * drug type * drug order (all $p > .17$). Taken together, these results show that potential drug order and learning effects were negligible.

Encoding

A whole-brain analysis was performed for the contrast Learning>Resting at a threshold level set at $p < .05$ (corrected for FWE). For Learning compared with Resting baseline, significant and extensive activation was seen in widespread networks including bilateral occipital lobe, gyrus parahippocampalis, SMA and left dorsolateral PFC (DLPFC) across all participants (Figure S1A). The opposite contrast Resting>Learning showed significant activation within the default mode network including prefrontal, parietal and temporo-insular areas. All findings are summarized in Table S4.

Recognition

To demonstrate recognition processing of all participants, the average BOLD signal of 39 participants during recognition was contrasted with the BOLD signal during the control condition (Recognition>Control, $p < .001$, unc., cluster size > 23 Voxels). This revealed significant task-related activations in widespread cortical and subcortical networks including the parietal lobe, left frontal lobe, and bilateral occipital lobe. Furthermore, bilateral activations were found in the caudate nucleus, anterior cingulate cortex (ACC), and middle temporal regions (Table S5, Figure S1B). On the other hand, Control>Recognition revealed activations in ACC, gyrus supramarginalis, precuneus, bilateral hippocampus, left insula, middle temporal gyrus, and posterior cingulate cortex (PCC).

Tables

Table S1. Imaging studies comparing MPH and PLA in healthy adults

Study	N	Method	Dose	Cognitive domain	Test paradigm	Behavioural effects	Imaging effects
Memory							
(Mehta et al., 2000)	10	PET	40 mg	Working memory	Spatial search task	Fewer errors in between search, but no difference to PLA in within-search	*MPH X Task* Activation in DLPFC (l), PPC (l) , SMA (l) *MPH > Placebo* Increases of rCBF in cerebellum (r), Decreases rCBF in frontal (l) and temporal regions (r)
(Honey et al., 2003)	23	fMRI	20 mg	Object learning	Delayed match task	No effect	*MPH > Placebo* Decrease of functional connectivity between caudate nucleus and midbrain No effect for caudate-thalamus correlation
(Dodds et al., 2008)	20	fMRI	60 mg	Working memory, Performance maintenance	Reversal learning (RL), Task Switching (TS)	No effect	*MPH X reversal errors:* decrease in putamen, cuneus, precentral gyrus *MPH X non-switch errors* Signal decrease in VLPFC, ACC
(Clatworthy et al., 2009)	9	PET	60 mg	Working memory	Reversal Learning (RL), spatial working memory (SWM)	No effect	*MPH X RL*: decrease in caudate nucleus *MPH X SWM*: Activation in ventral Striatum
(Tomasi et al., 2011)	32	fMRI	20 mg	Working memory, Visual attention	n-back task, visual tracking	*Accuracy* No effect *RT* MPH>PLA	*MPH X Task:* no effect *MPH > Placebo:* activations in parietal cortex, PFC Deactivations in PCC, Insula
(Wagner et al., 2017)	26	fMRI	20 mg	Associative memory	Associative memory task	No effect	*No differential activation during memory retrieval after 72h*
(Marquand et al., 2011)	15	fMRI	30 mg	Working memory	Spatial delay match task	No effect	*MPH X Task* With reward: Deactivations in default-mode-network (PCC, precuneus, VMPFC) Without Reward: Activations in PCC, precuneus and VMPFC during encoding only

(Gorka et al., 2020)	53	fMRI	20mg	Working memory	N-back task	No effect	*MPH > Placebo* Reduction of intra-thalamic connectivity between lateral PFC and motor and somatosensory thalamic sub-regions
Attention							
(Rao et al., 2000)	6	fMRI	20 mg	Motor response	Finger tapping	No effect	No effect
(Müller et al., 2005)	12	fMRI	20 mg	Visual attention Movement preparation	Motor reaction task	No effect	*MPH X Task* Activation in precentral gyrus, inferior parietal gyrus, precuneus
(Udo de Haes et al., 2007)	7	PET	0.25 mg/Kg	Sustained attention	Continuous performance task	Not reported	*MPH X Task* Activations in ACC, temporal poles, supplementary motor area, cerebellum Deactivations in superior temporal gyri, right medial frontal gyrus and right inferior parietal cortex
(del Campo et al., 2013)	16	PET	0.5 mg/Kg	Sustained attention	Rapid visual information processing task	Baseline effects of MPH: low performers get enhanced through drug	*MPH > Placebo* Increase in extracellular DA in SN/VTA, ventral striatum
(Ivanov et al., 2014)	16	fMRI	0.5 mg/Kg	Information processing	Anticipation, conflict, reward paradigm	Increased accuracy	*MPH > Placebo* *Signal decrease in attention-activation systems irrespective of the reward cue, and in components of the reward–motivation system, particularly the insula, during reward trials.*
(Kasparbauer et al., 2016)	27	fMRI	40 mg	Attention	Smooth pursuit eye movement task	No effect	*No effect*
(Farr et al., 2014)	48	fMRI	45 mg	Saliency processing	Stop-Signal-Task (SST)	No effect	*MPH X SST* Activation in bilateral caudate nucleus, motor cortex, right inf. PFC, cerebellum
Executive Functions							
(Schlösser et al., 2009)	12	fMRI	40 mg	Decision making, Uncertainty	Reinforcement learning, uncertainty	No effect	*MPH X Task* Activations in parahippocampal Gyrus, ACC, cerebellum, precentral gyrus *Placebo X Task:* Parietal cortex, PCC

(Pauls et al., 2012)	16	fMRI	40 mg	Response inhibition	Stop-Signal Task with and without attention capturing	Effect only in modified SST No effect in accuracy	*MPH X SST* Deactivations in right inferior frontal gyrus and insula during successful and failed inhibitions *MPH X Error tria*ations in ACC, medial frontal gyrus,
(Costa et al., 2013)	52	fMRI	40 mg	Error Processing, Response inhibition	Go/No-Go Task, Stop-Signal-Task (SST)	No effect	*MPH X Go/No-go Task:* Activation only during unsuccessful inhibition in right putamen *MPH X SST:* No effect
(Moeller et al., 2014)	15	fMRI	20 mg	Error processing	Stroop test	No effect	*MPH X Error>correct response* Deactivation in ACC
(Nandam et al., 2014)	27	fMRI	30 mg	Response Inhibition	Go/No-Go Task	No effect	*MPH > Placebo* *Activation in the pregenual cingulate (dorsal anterior cingulate), inferior frontal (r), middle frontal (l), angular (l) and superior (r) temporal gyri and caudate (r).*
(Schmidt et al., 2017)	21	fMRI	60 mg	Response inhibition	Go/No-Go Task	Improved inhibitory performance	*MPH > Placebo* Activation in middle frontal gyrus (r), middle/superior temporal gyrus, inferior parietal lobule, presupplementary motor area, and ACC.
(Evers et al., 2017)	20	fMRI	40 mg	Reward processing	Gambling task	Reduced reaction time	*MPH > Placebo* *Reward expectancy-related activation in the ventral striatum.*
(Goldstein et al., 2010)	14	fMRI	20 mg	Error and Reward Processing	Stroop test	Decreased commission errors	*MPH > Placebo* Activations in the DLPFC and fusiform gyrus during task
Mood							
(Schmidt et al., 2018)	22	fMRI	60 mg	Negative emotion processing	Response to fearful faces	No effect	No effect
Resting State							
(Wang et al., 1994)	5	PET	0.5 mg/Kg	-	-	-	Global decreases in cerebral blood flow (CBF), no regional differences
(Volkow et al., 2001)	11	PET	60 mg	-	-	-	ROI Striatum: Increase in DA ROI Cerebellum: No effect
(Ramaekers et al., 2013)	20	fMRI	40 mg	-	-	-	ROI analysis: Reduced FC between the NAcc and the basal ganglia. Decreased FC between the NAcc and the medial prefrontal cortex (mPFC) and the temporal cortex. No change in the FC between the medial dorsal nucleus and the limbic circuit.

(Mueller et al., 2014)	54	fMRI	40 mg	-	-	-	Increased connectivity between the dorsal attention network and the thalamus. Increased connectivity between sensory-motor and visual cortex regions. Decreased connectivity between cortical and subcortical components of cortico-striato-thalamo-cortical circuits (CST).
(Zhu et al., 2013)	18	RS fMRI	20 mg	-	Go/No-Go Task (after scanning)	No effect in Go/No-Go Task	Increase in Regional homogeneity (ReHo) in middle and superior temporal gyrus (l, BA 39) Decrease in ReHo in lingual gyrus (l, BA 19)
(Wang et al., 2019)	23	PET	0.5mg/ Kg	Effect of Expectation	-	-	Increased DA-release in bilateral putamen, in bilateral NAcc and caudate nucleus Decreased D2R in striatum
(Demiral et al., 2019)	16	fMRI, PET	0.5mg/ Kg	-	-	-	fMRI: Increased RFC between sensory and motor thalamic seeds and right cerebellum Increased negative RFC between NAcc and premotor thalamic seed region PET: Increased thalamic glucose metabolism in all seed regions
Motivation							
(Hofmans et al., 2020)	46	PET	20mg	Cognitive motivation	Cognitive effort discounting choice task	Higher proportion of choices of cognitive effort over leisure MPH>PLA	Interaction between MPH and dopamine synthesis capacity in NAcc and putamen

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Table S2. Imaging studies comparing MOD and PLA in healthy adults

Study	N	Method	Dose	Cognitive domain	Test paradigm	Behavioural effects	Imaging effects
Working memory & Executive functions							
(Minzenberg et al., 2008)	21	fMRI	200 mg	Executive functioning	Task switching	Accuracy increase in low-performers, RT cost correlated to drug dose	*MOD>Placebo* Deactivations in bilateral pons *MPH X Task* Activations in bilateral pons and PFC
(Ikeda et al., 2017)	23	fMRI	200 mg	Attention	Flanker task	Increased alerting performance	*MOD>Placebo* Activations in middle and inferior occipital gyri
(Rasetti et al., 2010)	19	fMRI	100 mg/d for 7d	Working memory, Visual attention, Fear processing	N-back-task, Variable-attention-task (VAT), Face-matching-task (FMT)	No effect	*MOD X FMT*: Deactivation in amygdala (r) *MOD X N-Back* Deactivations in PFC (r), *MOD X VAT:* Deactivations in ACC
(Ghahremani et al., 2011)	19	fMRI	200 mg	Working memory	Reversal learning	No effect	*MOD > Placebo* bilateral ventral occipito-temporal cortex, lateral occipital cortex, and superior parietal regions, inferior frontal (r) and middle frontal gyri (r)
(Esposito et al., 2013)	26	RS fMRI	100 mg	Fluid intelligence	Resting State, Raven's matrices test	Drug effect for medium difficulty, low and high difficulty were not affected by drug	Activations in frontal parietal control (FPC) and dorsal attention network (DAN) networks No activations found in salience network (SN) and no effect in functional connectivity (FC)
(Ngo et al., 2019)	18	fMRI	200 mg	Moral decision making	Moral dilemma decision task	Increased moral decisions	MOD>Placebo Activations in bilateral medial PFC, the insula, and the precuneus
(Schmaal et al., 2013)	16	fMRI	200 mg	Response Inhibition	Stop-Signal-Task	RT decrease in Go Trials	No effect
(Schmidt et al., 2017)	21	fMRI	600 mg	Response inhibition	Go/No-Go Task	Improved inhibitory performance	*MOD > Placebo* Activation in middle frontal gyrus (r) and superior/inferior parietal lobule.

(Schmaal et al., 2014)	16	fMRI	200 mg	Decision making	Delay-discounting-task	No effect	No effect
Mood & Reward							
(Volkow et al., 2009)	10	PET	200 mg/ 400 mg	Mood & emotion	Visual analogue scales prior and after scanning	No effect	Increased extracellular DA and occupancy of DAT in striatum and Ncl. Accumbens, no differences in dosing
(Goudriaan et al., 2013)	16	fMRI	200 mg	Addiction	Visual observation of cocaine Stimuli	No effect	No effect
(Schmidt et al., 2018)	22	fMRI	600 mg	Negative emotion processing	Response to fearful faces	No effect	*MOD > Placebo* Activation in amygdala, ACC, pallidum, putamen (r), SMA (r), caudate nucleus (l) and thalamus (l).
(Funayama et al., 2014)	20	fMRI	200 mg	Reward processing	Monetary incentive delay task	Decrease in commission errors	*MPH X Task* No effect on whole brain level ROI Ncl accumbens: only activation during highest incentive
Sensory Functioning							
(Ellis et al., 1999)	12	fMRI	400 mg	Sensory function	Visual and auditory stimulation	No effect	*MOD X Attention* Low baseline increases amount of voxels, high baseline decreases amount of activated voxels.
(Joo et al., 2008)	21	SPECT	400 mg	Wakefulness	Visual and acoustic reaction tasks	Reduced sleepiness, No effect in RTs	*MOD>BASELINE* Increase of CBF in bilateral thalami, dorsal pons MOD>PLA Activation of CBF in bilateral fronto-polar, orbitofrontal, superior frontal, middle frontal gyri, short insular gyri, left cingulate gyrus, left middle/inferior temporal gyri, left parahippocampal gyrus, and left pons
(Minzenberg et al., 2011)	18	RS fMRI	200 mg	Resting	Resting state, visual sensorimotor task	RT correlated with drug dependent deactivations in vmPFC	*MOD X Task* Deactivations in vmPFC, PCC and left Inferior parietal lobe (IPL)
Resting State							
(Kim et al., 2014)	10	PET	200 mg/ 300 mg	-	-	-	Enhanced DAT binding in striatum

(Punzi et al., 2017)	24	RS fMRI	100 mg	-	-	-	Enhanced FC between V1 and cerebellar (Crus I, Crus II, VIIIa lobule) and frontal (right inferior frontal sulcus and left middle frontal gyrus) regions.
(Cera et al., 2014)	26	RS fMRI	100 mg	-	-	-	Increased FC in putamen, left parahippocampus, left posterior insula and MCC

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Table S3. Imaging studies comparing CAF and PLA in healthy adults

Study	N	Method	Dose	Cognitive domain	Test paradigm	Behavioural effects	Imaging effects
Working memory							
(Koppelstaetter et al., 2008)	15	fMRI	100 mg	Working memory	n-back task	No effect	*Task X CAF* Activations in bilateral medial frontopolar cortex (BA 10), right anterior cingulate (BA 32)
(Klaassen et al., 2013)	21	fMRI	100 mg	Working memory	Sternberg Task	No effect in accuracy and RT	*CAF X Task* Encoding: activation in DLPFC (r) Maintenance: deactivation in thalamus (l) Retrieval: no drug effect
(Haller et al., 2013)	24	fMRI	200 mg	Working memory	2-back Task	No effect	*CAF X Task* Activations in bilateral striatum, middle and inferior frontal gyrus (r), bilateral insula, superior and inferior parietal lobule (l), bilateral cerebellum, Deactivations in bilateral superior parietal *FC analysis* CAF dependent enhanced connectivity between PFC, vPMC, the SMA, the parietal cortex as well as visual areas
(Haller et al., 2014)	15	fMRI	200 mg	Working memory	2-Back Task	No effect	*CAF X Task* Activations in bilateral striatum, middle and inferior frontal gyrus (r), bilateral insula, superior and inferior parietal lobule (l) *FC Analysis* No CAF effect
(Heilbronner et al., 2015)	10	NIRS	200 mg	Working memory	2-back Task	No effect	General decrease of the HbO response after CAF intake During Task: Increase of the HbR response of the left IFC
Visual stimulation							
(Mulderink et al., 2002)	18	fMRI	200 mg	Sensory function	Checkerboard observation and	No effect	*BOLD Signal change CAF>Baseline*

					finger movements		Activation in motor cortex (M1) around 37%, activation in visual cortex (V1) region around 26% No whole brain data reported
(Laurienti et al., 2002)	20	fMRI	250 mg	passive sensory stimulation	Checkerboard observation	-	*CAF>Placebo* - *High vs. Low Consumers* Increased BOLD signal in high dose subj. BOLD signal correlates with prior coffee consumption
(Laurienti et al., 2003)	19	fMRI	250 mg	passive sensory stimulation	Checkerboard observation	-	*CAF>Placebo* Decrease in CBF, no correlation to BOLD signal was found
(Liu et al., 2004)	5	fMRI	200 mg	Visual stimulation	Checkerboard observation	-	*CAF>Placebo* Decrease in CBF during rest, high variance in visual response amplitude within participants
(Perthen et al., 2008)	10	fMRI	250 mg	Visual stimulation	Checkerboard	-	Reduction in rCBF in visual cortex
(Grichisch et al., 2012)	8	fMRI	200 mg	Visual stimulation	Checkerboard	-	Reduction in rCBF in visual cortex, no change in BOLD response
Attention							
(Liau et al., 2008)	10	fMRI	200 mg	Attention motor reaction	Checkerboard Finger tapping after cue	-	*CAF>Placebo* Decreases in CBF and Signal-to-Noise ratio (SNR), no effect in BOLD
(Chen and Parrish, 2009)	27	fMRI	1 mg/kg 2,5 mg/kg 5 mg/kg	Visual attention motor Reaction	Checkerboard Finger Tapping	-	Reduction in rCBF during resting state Increase in %CBF and %BOLD responses during task in motor and visual cortex
(Serra-Grabulosa et al., 2010)	10	fMRI	75mg	Sustained attention	Continuous performance test	No effect	*CAF>Placebo* No effect
(Diukova et al., 2012)	14	fMRI EEG	250 mg	Motor reaction Visual attention Acoustic attention	Finger tapping Checkerboard Auditory oddball task	Oddball: less missed responses, no effect on false alarms or RT	*CAF X Visual Task* Reductions in V1 and superior temporal lobe (l) *CAF X Motor Task* Deactivations in left sensorimotor cortex *CAF X Oddball (Target>Non-Target)* Activations in superior frontal gyrus, frontal pole and para-cingulate gyrus
(Park et al., 2014)	14 7	fMRI PET	200 mg	Attention Motor reaction	Finger tapping after cue	-	*fMRI* *CAF>Placebo*

							Activations in Cerebellum (l), putamen, thalamus, insula, precentral gyrus (r) Deactivations in VMPFC, precuneus, posterior lateral cortex (l) PET (glucose metabolism) Deactivations in posterior medial cortex, striatum, insula and pallidum
(Bendlin et al., 2007)	21	fMRI	~ 222 mg	Novelty processing alertness	Word stem completion task	No effect	No effect
(Addicott et al., 2012)	45 17	fMRI	250 mg	Reaction Time	Simple reaction time task	No effect	Reduction in BOLD time course parameters TTP, FWHM, CBF Decreased BOLD contrast activation
(Kahathuduwa et al., 2018)	9	fMRI	160mg	Reaction time	Visual color stimulus discrimination task	No effect	No effect in BOLD responses Response to distractors: decreased mind wandering, decreased early visual attention to target stimuli
Resting State[1]							
(Wu et al., 2014)	17	RS fMRI	200 mg	Resting state	-	-	CAF decreases FC in motor cortex and visual cortex, no difference for DMN
(Volkow et al., 2015)	20	PET	300 mg	Resting state	-	-	CAF increases D2/D3R receptor availability in putamen and ventral striatum
(Kaasinen et al., 2004)	8	PET	200 mg	Resting state	-	-	Decrease in thalamic [11C]raclopride binding potential. Trend level increase in ventral striatum [11C]raclopride binding potential
Mood							
(Smith et al., 2012)	14	fMRI	250 mg	Emotional Face Processing	Emotional Face Processing Task, Simple Visual Task	Increased self-rated anxiety and blood pressure (angry/fearful faces)	CAF induces threat-related midbrain-periaqueductal gray activation (angry/fearful faces > happy faces). Abolishment of threat-related medial prefrontal cortex wall activation

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Table S4. Peak Voxels of activated clusters during learning and resting condition

Region	BA	MNI coordinates			Laterality	*t*-score	*k*
		X	Y	Z			
Learning>Resting							
Calcarine gyrus	17	12	-91	5	R/L	11.36	268
SMA	6	-6	8	59	R/L	10.34	126
Inferior frontal gyrus	44	-48	8	29	L	10.15	358
Inferior temporal gyrus	37	-42	-64	-10	L	9.95	166
Fusiform gyrus	20	-30	-34	-22	L	9.57	88
Precentral gyrus	6	-42	-1	53	L	7.27	61
Resting>Learning							
Middle cingulate cortex	6	3	-19	41	R/L	10.64	1220
Inferior parietal lobe (PFcm)	40	51	-28	23	R/L	9.56	485
Middle orbitofrontal cortex	32	3	26	-10	R/L	8.56	173
Insula	13	-42	-11	11	L	8.31	107
Superior frontal gyrus	9	21	35	35	R	8.24	125

BA = Brodmann area, $p < 0.05$ (FWE corrected), N = 39; FWE = Family-wise error corrected, R = right, L = left.

Table S5. Peak Voxels of activated clusters during recognition and control condition

Region	BA	MNI coordinates			Laterality	*t*-score	*k*
		X	Y	Z			
Recognition>Control							
Inferior parietal lobe	40	39	-40	41	R/L	6.36	1835
Caudate nucleus		-18	14	8	L	5.33	77
Middle temporal gyrus	41	-48	-37	-7	L	5.86	103
Precentral gyrus	44	-36	8	32	R/L	5.73	344
Inferior occipital gyrus	18	-33	-85	-10	L	4.66	86
Precuneus	18	9	-87	17	R/L	4.87	305
Medial cingulate cortex	9	-3	29	35	R/L	4.15	41
Control>Recognition							
Rectal Gyrus	11	-3	32	-16	R/L	6.27	228
Insula	13	42	-10	-4	R/L	6.48	697
Inferior Parietal Cortex (PF)	2	63	-28	35	R/L	6.44	598
Paracentral lobus	3a	15	-37	50	R/L	5.77	573
Gyrus parahippocampalis	36	33	-25	-19	R	5.95	57
Hippocampus	34	54	-58	11	R/L	5.69	57
Posterior cingulate cortex	18	9	-49	23	R/L	4.76	44
Hippocampus	34	-24	-13	-19	L	4.70	28
Calcarine Gyrus	18	24	-52	8	R	4.06	26

BA = Brodmann area, $p < .001$, N = 39, FWHM 8.6411 8.5912 8.3449, two-tailed, $k > 23$.

Figures

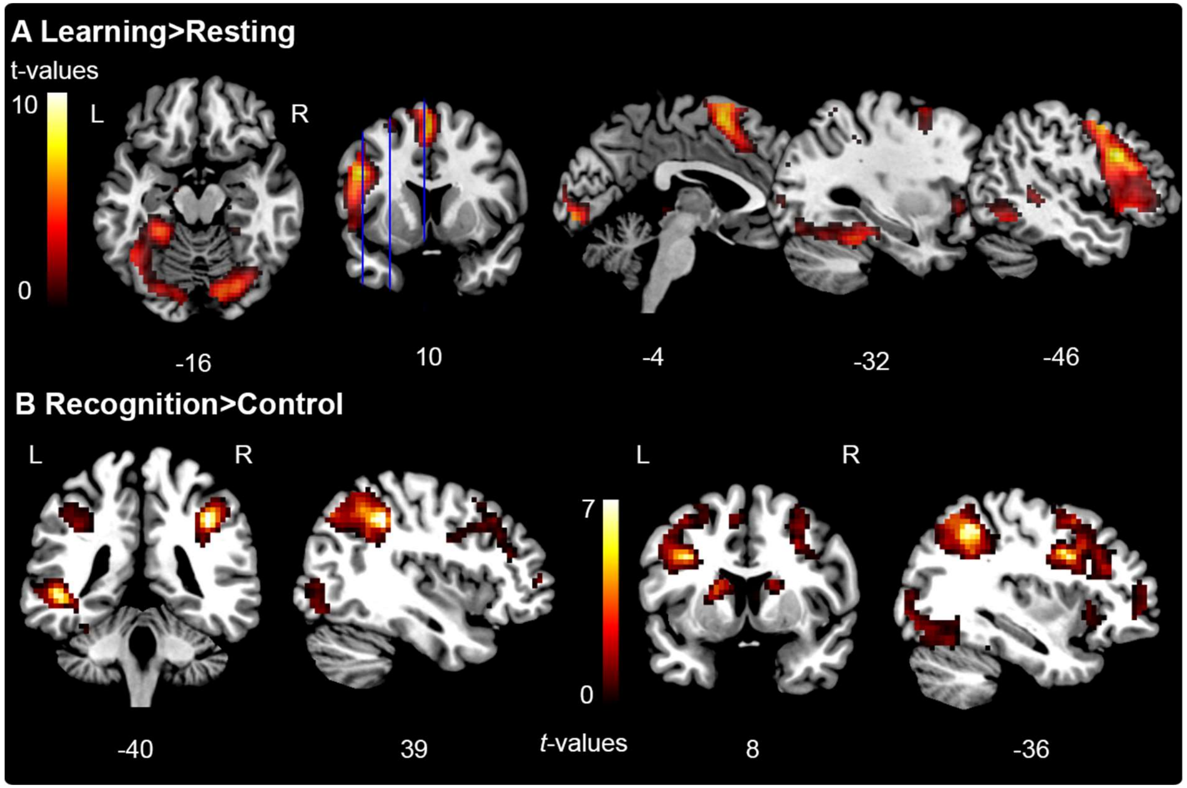

Figure S1. BOLD signal changes during learning and recognition task. Signal increase during (A) encoding, $p < .05$, FWE corrected, and (B) recognition, $p < .001$, FWHM 8.7394 8.6916 8.3495, two-tailed, $k > 23$ in 39 participants. L = left, R = right.

References

Addicott, M.A., Peiffer, A.M., Laurienti, P.J., 2012. The Effects of Dietary Caffeine Use and Abstention on Blood Oxygen Level-Dependent Activation and Cerebral Blood Flow. J Caffeine Res 2, 15-22.

Bendlin, B.B., Trouard, T.P., Ryan, L., 2007. Caffeine attenuates practice effects in word stem completion as measured by fMRI BOLD signal. Hum Brain Mapp 28, 654-662.

Cera, N., Tartaro, A., Sensi, S.L., 2014. Modafinil alters intrinsic functional connectivity of the right posterior insula: a pharmacological resting state fMRI study. PLoS One 9, e107145.

Chen, Y., Parrish, T.B., 2009. Caffeine dose effect on activation-induced BOLD and CBF responses. Neuroimage 46, 577-583.

Clatworthy, P.L., Lewis, S.J., Brichard, L., Hong, Y.T., Izquierdo, D., Clark, L., Cools, R., Aigbirhio, F.I., Baron, J.C., Fryer, T.D., Robbins, T.W., 2009. Dopamine release in dissociable striatal subregions predicts the different effects of oral methylphenidate on reversal learning and spatial working memory. J Neurosci 29, 4690-4696.

Costa, A., Riedel, M., Pogarell, O., Menzel-Zelnitschek, F., Schwarz, M., Reiser, M., Moller, H.J., Rubia, K., Meindl, T., Ettinger, U., 2013. Methylphenidate effects on neural activity during response inhibition in healthy humans. Cereb Cortex 23, 1179-1189.

del Campo, N., Fryer, T.D., Hong, Y.T., Smith, R., Brichard, L., Acosta-Cabronero, J., Chamberlain, S.R., Tait, R., Izquierdo, D., Regenthal, R., Dowson, J., Suckling, J., Baron, J.C., Aigbirhio, F.I., Robbins, T.W., Sahakian, B.J., Muller, U., 2013. A positron emission tomography study of nigro-striatal dopaminergic mechanisms underlying attention: implications for ADHD and its treatment. Brain 136, 3252-3270.

Demiral , S.B., Tomasi, D., Wiers, C.E., Manza, P., Shokri-Kojori, E., Studentsova, Y., Wang, G.J., Volkow, N.D., 2019. Methylphenidate's effects on thalamic metabolism and functional connectivity in cannabis abusers and healthy controls. Neuropsychopharmacology 44, 1389-1397.

Diukova, A., Ware, J., Smith, J.E., Evans, C.J., Murphy, K., Rogers, P.J., Wise, R.G., 2012. Separating neural and vascular effects of caffeine using simultaneous EEG-FMRI: differential effects of caffeine on cognitive and sensorimotor brain responses. Neuroimage 62, 239-249.

Dodds, C.M., Muller, U., Clark, L., van Loon, A., Cools, R., Robbins, T.W., 2008. Methylphenidate has differential effects on blood oxygenation level-dependent signal related to cognitive subprocesses of reversal learning. J Neurosci 28, 5976-5982.

Ellis, C.M., Monk, C., Simmons, A., Lemmens, G., Williams, S.C., Brammer, M., Bullmore, E., Parkes, J.D., 1999. Functional magnetic resonance imaging neuroactivation studies in normal subjects and subjects with the narcoleptic syndrome. Actions of modafinil. J Sleep Res 8, 85-93.

Esposito, R., Cilli, F., Pieramico, V., Ferretti, A., Macchia, A., Tommasi, M., Saggino, A., Ciavardelli, D., Manna, A., Navarra, R., Cieri, F., Stuppia, L., Tartaro, A., Sensi, S.L., 2013. Acute effects of modafinil on brain resting state networks in young healthy subjects. PLoS One 8, e69224.

Evers, E.A., Stiers, P., Ramaekers, J.G., 2017. High reward expectancy during methylphenidate depresses the dopaminergic response to gain and loss. Soc Cogn Affect Neurosci 12, 311-318.
Farr, O.M., Hu, S., Matuskey, D., Zhang, S., Abdelghany, O., Li, C.S., 2014. The effects of methylphenidate on cerebral activations to salient stimuli in healthy adults. Exp Clin Psychopharmacol 22, 154-165.
Funayama, T., Ikeda, Y., Tateno, A., Takahashi, H., Okubo, Y., Fukayama, H., Suzuki, H., 2014. Modafinil augments brain activation associated with reward anticipation in the nucleus accumbens. Psychopharmacology (Berl) 231, 3217-3228.
Ghahremani, D.G., Tabibnia, G., Monterosso, J., Hellemann, G., Poldrack, R.A., London, E.D., 2011. Effect of modafinil on learning and task-related brain activity in methamphetamine-dependent and healthy individuals. Neuropsychopharmacology 36, 950-959.
Goldstein, R.Z., Woicik, P.A., Maloney, T., Tomasi, D., Alia-Klein, N., Shan, J., Honorio, J., Samaras, D., Wang, R., Telang, F., Wang, G.J., Volkow, N.D., 2010. Oral methylphenidate normalizes cingulate activity in cocaine addiction during a salient cognitive task. Proc Natl Acad Sci U S A 107, 16667-16672.
Gorka, A.X., Lago, T.R., Balderston, N., Torrisi, S., Fuchs, B., Grillon, C., Ernst, M., 2020. Intrinsic connections between thalamic sub-regions and the lateral prefrontal cortex are differentially impacted by acute methylphenidate. Psychopharmacology (Berl) 237, 1873-1883.
Goudriaan, A.E., Veltman, D.J., van den Brink, W., Dom, G., Schmaal, L., 2013. Neurophysiological effects of modafinil on cue-exposure in cocaine dependence: a randomized placebo-controlled cross-over study using pharmacological fMRI. Addict Behav 38, 1509-1517.
Grichisch, Y., Cavusoglu, M., Preissl, H., Uludag, K., Hallschmid, M., Birbaumer, N., Haring, H.U., Fritsche, A., Veit, R., 2012. Differential effects of intranasal insulin and caffeine on cerebral blood flow. Hum Brain Mapp 33, 280-287.
Haller, S., Montandon, M.L., Rodriguez, C., Moser, D., Toma, S., Hofmeister, J., Sinanaj, I., Lovblad, K.O., Giannakopoulos, P., 2014. Acute caffeine administration effect on brain activation patterns in mild cognitive impairment. J Alzheimers Dis 41, 101-112.
Haller, S., Rodriguez, C., Moser, D., Toma, S., Hofmeister, J., Sinanaj, I., Van De Ville, D., Giannakopoulos, P., Lovblad, K.O., 2013. Acute caffeine administration impact on working memory-related brain activation and functional connectivity in the elderly: a BOLD and perfusion MRI study. Neuroscience 250, 364-371.
Heilbronner, U., Hinrichs, H., Heinze, H.J., Zaehle, T., 2015. Caffeine differentially alters cortical hemodynamic activity during working memory: a near infrared spectroscopy study. BMC Res Notes 8, 520.
Hofmans, L., Papadopetraki, D., van den Bosch, R., Määttä, J.I., Froböse, M.I., Zandbelt, B.B., Westbrook, A., Verkes, R.J., Cools, R., 2020. Methylphenidate boosts choices of mental labor over leisure depending on striatal dopamine synthesis capacity. Neuropsychopharmacology 45, 2170-2179.
Honey, G.D., Suckling, J., Zelaya, F., Long, C., Routledge, C., Jackson, S., Ng, V., Fletcher, P.C., Williams, S.C., Brown, J., Bullmore, E.T., 2003. Dopaminergic drug effects on physiological connectivity in a human cortico-striato-thalamic system. Brain 126, 1767-1781.

Ikeda, Y., Funayama, T., Tateno, A., Fukayama, H., Okubo, Y., Suzuki, H., 2017. Modafinil enhances alerting-related brain activity in attention networks. Psychopharmacology (Berl) 234, 2077-2089.
Ivanov, I., Liu, X., Clerkin, S., Schulz, K., Fan, J., Friston, K., London, E.D., Schwartz, J., Newcorn, J.H., 2014. Methylphenidate and brain activity in a reward/conflict paradigm: role of the insula in task performance. Eur Neuropsychopharmacol 24, 897-906.
Joo, E.Y., Tae, W.S., Jung, K.Y., Hong, S.B., 2008. Cerebral blood flow changes in man by wake-promoting drug, modafinil: a randomized double blind study. J Sleep Res 17, 82-88.
Kaasinen, V., Aalto, S., Någren, K., Rinne, J.O., 2004. Dopaminergic effects of caffeine in the human striatum and thalamus. Neuroreport 15, 281-285.
Kahathuduwa, C.N., Dhanasekara, C.S., Chin, S.H., Davis, T., Weerasinghe, V.S., Dassanayake, T.L., Binks, M., 2018. l-Theanine and caffeine improve target-specific attention to visual stimuli by decreasing mind wandering: a human functional magnetic resonance imaging study. Nutr Res 49, 67-78.
Kasparbauer, A.M., Meyhofer, I., Steffens, M., Weber, B., Aydin, M., Kumari, V., Hurlemann, R., Ettinger, U., 2016. Neural effects of methylphenidate and nicotine during smooth pursuit eye movements. Neuroimage 141, 52-59.
Kim, W., Tateno, A., Arakawa, R., Sakayori, T., Ikeda, Y., Suzuki, H., Okubo, Y., 2014. In vivo activity of modafinil on dopamine transporter measured with positron emission tomography and [18F] FE-PE2I. International Journal of Neuropsychopharmacology 17, 697-703.
Klaassen, E.B., de Groot, R.H., Evers, E.A., Snel, J., Veerman, E.C., Ligtenberg, A.J., Jolles, J., Veltman, D.J., 2013. The effect of caffeine on working memory load-related brain activation in middle-aged males. Neuropharmacology 64, 160-167.
Koppelstaetter, F., Poeppel, T.D., Siedentopf, C.M., Ischebeck, A., Verius, M., Haala, I., Mottaghy, F.M., Rhomberg, P., Golaszewski, S., Gotwald, T., Lorenz, I.H., Kolbitsch, C., Felber, S., Krause, B.J., 2008. Does caffeine modulate verbal working memory processes? An fMRI study. Neuroimage 39, 492-499.
Laurienti, P.J., Field, A.S., Burdette, J.H., Maldjian, J.A., Yen, Y.F., Moody, D.M., 2002. Dietary caffeine consumption modulates fMRI measures. Neuroimage 17, 751-757.
Laurienti, P.J., Field, A.S., Burdette, J.H., Maldjian, J.A., Yen, Y.F., Moody, D.M., 2003. Relationship between caffeine-induced changes in resting cerebral perfusion and blood oxygenation level-dependent signal. AJNR Am J Neuroradiol 24, 1607-1611.
Liau, J., Perthen, J.E., Liu, T.T., 2008. Caffeine reduces the activation extent and contrast-to-noise ratio of the functional cerebral blood flow response but not the BOLD response. Neuroimage 42, 296-305.
Liu, T.T., Behzadi, Y., Restom, K., Uludag, K., Lu, K., Buracas, G.T., Dubowitz, D.J., Buxton, R.B., 2004. Caffeine alters the temporal dynamics of the visual BOLD response. Neuroimage 23, 1402-1413.

Marquand, A.F., De Simoni, S., O'Daly, O.G., Williams, S.C., Mourao-Miranda, J., Mehta, M.A., 2011. Pattern classification of working memory networks reveals differential effects of methylphenidate, atomoxetine, and placebo in healthy volunteers. Neuropsychopharmacology 36, 1237-1247.
Mehta, M.A., Owen, A.M., Sahakian, B.J., Mavaddat, N., Pickard, J.D., Robbins, T.W., 2000. Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain. J Neurosci 20, RC65.
Minzenberg, M.J., Watrous, A.J., Yoon, J.H., Ursu, S., Carter, C.S., 2008. Modafinil shifts human locus coeruleus to low-tonic, high-phasic activity during functional MRI. Science 322, 1700-1702.
Minzenberg, M.J., Yoon, J.H., Carter, C.S., 2011. Modafinil modulation of the default mode network. Psychopharmacology (Berl) 215, 23-31.
Moeller, S.J., Honorio, J., Tomasi, D., Parvaz, M.A., Woicik, P.A., Volkow, N.D., Goldstein, R.Z., 2014. Methylphenidate enhances executive function and optimizes prefrontal function in both health and cocaine addiction. Cereb Cortex 24, 643-653.
Mueller, S., Costa, A., Keeser, D., Pogarell, O., Berman, A., Coates, U., Reiser, M.F., Riedel, M., Moller, H.J., Ettinger, U., Meindl, T., 2014. The effects of methylphenidate on whole brain intrinsic functional connectivity. Hum Brain Mapp 35, 5379-5388.
Mulderink, T.A., Gitelman, D.R., Mesulam, M.M., Parrish, T.B., 2002. On the use of caffeine as a contrast booster for BOLD fMRI studies. Neuroimage 15, 37-44.
Müller, U., Suckling, J., Zelaya, F., Honey, G., Faessel, H., Williams, S.C., Routledge, C., Brown, J., Robbins, T.W., Bullmore, E.T., 2005. Plasma level-dependent effects of methylphenidate on task-related functional magnetic resonance imaging signal changes. Psychopharmacology (Berl) 180, 624-633.
Nandam, L.S., Hester, R., Bellgrove, M.A., 2014. Dissociable and common effects of methylphenidate, atomoxetine and citalopram on response inhibition neural networks. Neuropsychologia 56, 263-270.
Ngo, T., Ghio, M., Kuchinke, L., Roser, P., Bellebaum, C., 2019. Moral decision making under modafinil: a randomized placebo-controlled double-blind crossover fMRI study. Psychopharmacology (Berl) 236, 2747-2759.
Park, C.A., Kang, C.K., Son, Y.D., Choi, E.J., Kim, S.H., Oh, S.T., Kim, Y.B., Park, C.W., Cho, Z.H., 2014. The effects of caffeine ingestion on cortical areas: functional imaging study. Magn Reson Imaging 32, 366-371.
Pauls, A.M., O'Daly, O.G., Rubia, K., Riedel, W.J., Williams, S.C., Mehta, M.A., 2012. Methylphenidate effects on prefrontal functioning during attentional-capture and response inhibition. Biol Psychiatry 72, 142-149.
Perthen, J.E., Lansing, A.E., Liau, J., Liu, T.T., Buxton, R.B., 2008. Caffeine-induced uncoupling of cerebral blood flow and oxygen metabolism: a calibrated BOLD fMRI study. Neuroimage 40, 237-247.
Punzi, M., Gili, T., Petrosini, L., Caltagirone, C., Spalletta, G., Sensi, S.L., 2017. Modafinil-Induced Changes in Functional Connectivity in the Cortex and Cerebellum of Healthy Elderly Subjects. Front Aging Neurosci 9, 85.

Ramaekers, J.G., Evers, E.A., Theunissen, E.L., Kuypers, K.P., Goulas, A., Stiers, P., 2013. Methylphenidate reduces functional connectivity of nucleus accumbens in brain reward circuit. Psychopharmacology (Berl) 229, 219-226.
Rao, S.M., Salmeron, B.J., Durgerian, S., Janowiak, J.A., Fischer, M., Risinger, R.C., Conant, L.L., Stein, E.A., 2000. Effects of methylphenidate on functional MRI blood-oxygen-level-dependent contrast. Am J Psychiatry 157, 1697-1699.
Rasetti, R., Mattay, V.S., Stankevich, B., Skjei, K., Blasi, G., Sambataro, F., Arrillaga-Romany, I.C., Goldberg, T.E., Callicott, J.H., Apud, J.A., Weinberger, D.R., 2010. Modulatory effects of modafinil on neural circuits regulating emotion and cognition. Neuropsychopharmacology 35, 2101-2109.
Repantis, D., Schlattmann, P., Laisney, O., Heuser, I., 2010. Modafinil and methylphenidate for neuroenhancement in healthy individuals: a systematic review. Pharmacological research 62, 187-206.
Schlösser, R.G., Nenadic, I., Wagner, G., Zysset, S., Koch, K., Sauer, H., 2009. Dopaminergic modulation of brain systems subserving decision making under uncertainty: a study with fMRI and methylphenidate challenge. Synapse 63, 429-442.
Schmaal, L., Goudriaan, A.E., Joos, L., Dom, G., Pattij, T., van den Brink, W., Veltman, D.J., 2014. Neural substrates of impulsive decision making modulated by modafinil in alcohol-dependent patients. Psychol Med 44, 2787-2798.
Schmaal, L., Joos, L., Koeleman, M., Veltman, D.J., van den Brink, W., Goudriaan, A.E., 2013. Effects of modafinil on neural correlates of response inhibition in alcohol-dependent patients. Biol Psychiatry 73, 211-218.
Schmidt, A., Muller, F., Dolder, P.C., Schmid, Y., Zanchi, D., Egloff, L., Liechti, M.E., Borgwardt, S., 2018. Acute Effects of Methylphenidate, Modafinil, and MDMA on Negative Emotion Processing. Int J Neuropsychopharmacol 21, 345-354.
Schmidt, A., Muller, F., Dolder, P.C., Schmid, Y., Zanchi, D., Liechti, M.E., Borgwardt, S., 2017. Comparative Effects of Methylphenidate, Modafinil, and MDMA on Response Inhibition Neural Networks in Healthy Subjects. Int J Neuropsychopharmacol 20, 712-720.
Serra-Grabulosa, J.M., Adan, A., Falcon, C., Bargallo, N., 2010. Glucose and caffeine effects on sustained attention: an exploratory fMRI study. Hum Psychopharmacol 25, 543-552.
Tomasi, D., Volkow, N.D., Wang, G.J., Wang, R., Telang, F., Caparelli, E.C., Wong, C., Jayne, M., Fowler, J.S., 2011. Methylphenidate enhances brain activation and deactivation responses to visual attention and working memory tasks in healthy controls. Neuroimage 54, 3101-3110.
Udo de Haes, J.I., Maguire, R.P., Jager, P.L., Paans, A.M., den Boer, J.A., 2007. Methylphenidate-induced activation of the anterior cingulate but not the striatum: a [15O]H2O PET study in healthy volunteers. Hum Brain Mapp 28, 625-635.
Volkow, N.D., Fowler, J.S., Logan, J., Alexoff, D., Zhu, W., Telang, F., Wang, G.J., Jayne, M., Hooker, J.M., Wong, C., Hubbard, B., Carter, P., Warner, D., King, P., Shea, C., Xu, Y., Muench, L., Apelskog-Torres, K., 2009. Effects of modafinil on dopamine and dopamine transporters in the male human brain: clinical implications. JAMA 301, 1148-1154.

Volkow, N.D., Wang, G., Fowler, J.S., Logan, J., Gerasimov, M., Maynard, L., Ding, Y., Gatley, S.J., Gifford, A., Franceschi, D., 2001. Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. J Neurosci 21, RC121.
Volkow, N.D., Wang, G.J., Logan, J., Alexoff, D., Fowler, J.S., Thanos, P.K., Wong, C., Casado, V., Ferre, S., Tomasi, D., 2015. Caffeine increases striatal dopamine D2/D3 receptor availability in the human brain. Transl Psychiatry 5, e549.
Wagner, I.C., van Buuren, M., Bovy, L., Morris, R.G., Fernandez, G., 2017. Methylphenidate during early consolidation affects long-term associative memory retrieval depending on baseline catecholamines. Psychopharmacology (Berl) 234, 657-669.
Wang, G.J., Volkow, N.D., Fowler, J.S., Ferrieri, R., Schlyer, D.J., Alexoff, D., Pappas, N., Lieberman, J., King, P., Warner, D., et al., 1994. Methylphenidate decreases regional cerebral blood flow in normal human subjects. Life Sci 54, PL143-146.
Wang, G.J., Wiers, C.E., Shumay, E., Tomasi, D., Yuan, K., Wong, C.T., Logan, J., Fowler, J.S., Volkow, N.D., 2019. Expectation effects on brain dopamine responses to methylphenidate in cocaine use disorder. Transl Psychiatry 9, 93.
Wu, W.C., Lien, S.H., Chang, J.H., Yang, S.C., 2014. Caffeine alters resting-state functional connectivity measured by blood oxygenation level-dependent MRI. NMR Biomed 27, 444-452.
Zhu, Y., Gao, B., Hua, J., Liu, W., Deng, Y., Zhang, L., Jiang, B., Zang, Y., 2013. Effects of methylphenidate on resting-state brain activity in normal adults: an fMRI study. Neurosci Bull 29, 16-27.