Brain and Cognition 154 (2021) 105802

Contents lists available at ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Memory enhancement with stimulants: Differential neural effects of methylphenidate, modafinil, and caffeine. A pilot study

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ARTICLE INFO

Keywords:
Declarative memory
Neuroenhancement
Memory enhancement
Methylphenidate
Modafinil
Caffeine
fMRI
Imaging

ABSTRACT

Human memory is susceptible to manipulation in many respects. While consolidation is well known to be prone to disruption, there is also growing evidence for the enhancement of memory function. Beside cognitive strategies and mnemonic training, the use of stimulants may improve memory processing in healthy adults. In this single-dose, double-blind, within-subject, randomized, placebo-controlled pilot study, 20 mg methylphenidate (N = 13) or 200 mg modafinil (N = 12) or 200 mg caffeine (N = 14) were administrated to in total 39 healthy participants while performing a declarative memory task. Each participant received only one substance and functional magnetic resonance imaging (fMRI) was used to assess drug-dependent memory effects of the substance for encoding and recognition compared to task-related activation under placebo. While methylphenidate showed some behavioral effect regarding memory recall performance, on the neural level, methylphenidate-dependent deactivations were found in fronto-parietal and temporal regions during recognition of previously learned words. No BOLD alterations were seen during encoding. Caffeine led to deactivations in the precentral gyrus during encoding whereas modafinil did not show any BOLD signal alterations at all. These results should be interpreted with caution since this a pilot study with several limitations, most importantly the small number of participants per group. However, our main finding of task-related deactivations may point to a drug-dependent increase of efficiency in physiological response to memory processing.

1. Introduction

Declarative memory is part of the human memory system. The three stages of the memorization process, encoding, consolidation, and recall or recognition (Riedel & Blokland, 2015), have their neuronal representation in a network including the medial temporal lobe, prefrontal, and cortical regions (Borst & Anderson, 2013; Lisman & Grace, 2005; Scimeca & Badre, 2012; Squire, Stark, & Clark, 2004). Thereby, catecholamines such as dopamine and noradrenaline seem to be crucial for the regulation of memory processing (Goldman-Rakic, 1995).

Memory consolidation, the process of long-term memory formation, further relies on a differential set of features such as pre-existing knowledge, as well as physiological and psychological function during learning (Squire, Genzel, Wixted, & Morris, 2015). Therefore, the consolidation of new memories is highly affected by the situational context, stress and arousal level (Kensinger & Corkin, 2003; Roozendaal & McGaugh, 2011). Thus, it can be assumed that consolidation of new information must be susceptible to manipulation in both directions: disruption and enhancement.

Noradrenaline and dopamine are the most frequently explored neurotransmitter with regard to memory enhancement (Riedel & Blokland, 2015). Several drugs that substantially affect the central dopamine system are thought to have enhancing properties, such as d-amphetamine, methylphenidate (MPH), tolcapone, and levodopa. Modafinil (MOD) as a dopamine and noradrenaline transporter inhibitor and, indirectly, caffeine (CAF) also influence central catecholamine

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https://doi.org/10.1016/j.bandc.2021.105802
Received 27 May 2021; Received in revised form 19 September 2021; Accepted 19 September 2021

metabolism (Ferre, 2016; Madras et al., 2006). However, drug dosage as well as characteristics of subjects and the examined cognitive domain of interest may interfere with the detection of performance effects (de Jongh, Bolt, Schermer, & Olivier, 2008). The investigated drugs of this study are further described below.

1.1. Methylphenidate

MPH is widely discussed as an enhancing drug (Compton, Han, Blanco, Johnson, & Jones, 2018; Repantis, Schlattmann, Laisney, & Heuser, 2010). Primarily prescribed for the treatment of attention-deficit/hyperactivity disorder (del Campo et al., 2013), MPH regulates catecholamine release in frontal-striatal pathways (Sharma & Couture, 2014). Animal studies on the effect of low-dose MPH show a positive effect on working memory (Arnsten & Dudley, 2005; Berridge et al., 2006), sustained attention (Andrzejewski et al., 2014), and long-term memory (Carmack, Block, Howell, & Anagnostaras, 2014). However, it is controversial whether MPH affects memory in healthy humans. While there are reports for positive MPH effects on working memory (Mehta et al., 2000), planning (Elliott et al., 1997) and memory function (Linssen, Sambeth, Vuurman, & Riedel, 2014), other studies could not identify significant effects of MPH on the recall of word lists (Hermens et al., 2007; Kuypers & Ramaekers, 2005). Other researchers have reported a baseline-dependent enhancing drug effect using a spatial association learning paradigm (I. C. Wagner, van Buuren, Bovy, Morris, & Fernandez, 2017). Depending on the cognitive task, MPH acts in a varied fashion in different brain regions in healthy adults (for a summary of published studies see Table S1). Until now, to our knowledge, no imaging study has focused on MPH effects on declarative memory in healthy individuals.

1.2. Modafinil

MOD is another stimulant that is supposingly being used as a cognitive enhancing substance (Repantis et al., 2010). Due to its wakefulness promoting properties it is approved for the treatment of narcolepsy (Dauvilliers, Billiard, & Montplaisir, 2003). MOD elevates extracellular catecholamine levels and activates indirectly the hypocretinergic system. It predominantly affects cortical areas of the frontal lobe and shows minor activity in subcortical sites (Minzenberg & Carter, 2008). Reports from animal studies exploring the effect of MOD are inconsistent (Wood, Sage, Shuman, & Anagnostaras, 2014). Memory processes specifically are enhanced in a very selective and dose-dependent fashion (Shuman, Wood, & Anagnostaras, 2009). In humans, a systematic review of sleep-deprivation studies suggests that MOD helped healthy individuals to maintain wakefulness, memory, and executive functions to a higher degree than placebo after one night of sleep deprivation (Battleday & Brem, 2015). The data for non-sleep deprived individuals are less clear. Among many null effect studies, some studies suggest that MOD could act as a cognitive enhancer in the domains of attention (Baranski, Pigeau, Dinich, & Jacobs, 2004; Makris, Rush, Frederich, Taylor, & Kelly, 2007) and memory processing (Müller et al., 2013; Randall et al., 2005). Of note, MOD's mode of action shows a diverse, task-dependent pattern (see Table S2). Up to now, no imaging studies on MOD's effect on verbal memory have been performed.

1.3. Caffeine

CAF is a natural stimulant occurring in several plants and commonly consumed in coffee, tea and soft drinks. In addition, it is discussed as an off-label treatment in several neurological disorders (Rivera-Oliver & Diaz-Rios, 2014). Besides its peripheral effects, CAF acts as a non-selective adenosine receptor antagonist (Takahashi, Pamplona, & Prediger, 2008) through which an upregulation of dopamine signaling in the putamen and ventral striatum is being achieved (Volkow et al., 2015). This mechanism may account for the increased arousal, locomotor behavior, and stimulation after CAF intake (Ullrich et al., 2015). These enhancing effects become more pronounced when individuals are sleep-deprived or lowered in alertness before CAF consumption (Smith, 2002). Summarizing previous data on the effects of CAF on cognition, Nehlig (2010) reported positive effects on working memory, mood and concentration, but not verbal memory function (Nehlig, 2010). In a study in which a single-dose was given after learning, Borota and colleagues (2014) found positive effects on memory consolidation but not on retrieval (Borota et al., 2014). This suggests that time of intake also influences the potential memory enhancing effect of CAF. Furthermore, Hameleers and colleagues (2000) reported positive effects of habitual CAF consumption on long-term memory whereas no effect on other cognitive functions was found (Hameleers et al., 2000). There are only a few studies using a demanding cognitive paradigm during imaging after CAF administration (see Table S3). Two fMRI studies on working memory in young healthy adults (Klaassen et al., 2013; Koppelstaetter et al., 2008) showed that CAF activates a fronto-parietal network, which also plays a key role in attention and memory retrieval (Fox et al., 2005).

By employing a double-blind, within-subject design alternating placebo and single-drug administration, the effect of three different stimulants (MPH, MOD, CAF) on memory performance in encoding, recognition, early and late recall was investigated. The behavioral results were already reported elsewhere (Repantis, Bovy, Ohla, Kuhn, & Dresler, 2021). Briefly, domain-specific and moderate effects were seen for MPH and CAF while no significant effect was seen for MOD in any assessment of the test battery. MPH slightly improved self-reported fatigue and late recall 24 h after learning, but not memory recognition nor immediate recall after learning word lists of a declarative memory task. After CAF intake, sustained attention was significantly improved. Here we report the results of functional imaging during task performance, which was used in order to investigate drug-induced changes of MPH, MOD and CAF on the neural level, expecting changes in brain function in the memory-associated brain areas that were discussed above.

2. Material and methods

2.1. Sample and questionnaires

Participants were recruited by means of online advertisement. Initially, 48 healthy male volunteers were included in the study (21 – 36 years, $M = 26.27$, $SD = 3.47$). Women were not recruited due to interactions of the female hormone cycle with brain structure and function as measured by MRI as well as cognitive tests (Lisofsky et al., 2015). All participants were right-handed (Edinburgh Handedness Inventory Score, $M = 84.0$, $SD = 20.0$) (Oldfield, 1971) and denied use of prescription medications, nicotine, or illicit substances. None of the participants were on a diet, nor engaged in shift work. Habitual consumption of small quantities of caffeinated drinks was allowed, whereas regular as well as excessive coffee and tea consumption (>4 cups/day) was not allowed. Further exclusion criteria were a history or presence of psychiatric or medical disorders as determined through medical examination, Beck Depression Inventory (BDI-V) (Schmitt, Altstötter-Gleich, Hinz, Maes, & Brähler, 2006) and the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). It was previously shown that memory function is generally associated to intellectual performance (Dresler et al., 2017). Therefore, all subjects were tested for group homogeneity and cognitive baseline performance (Table 1). Fluid intelligence was assessed with the Cultural Fair Test (Weiß, Albinus, & Arzt, 2006) as well as the digit-symbol-substitution-test (Wechsler, 1981). In addition, we administered a multiple choice lexicon intelligence test (Lehrl, 1999) to assess crystallized intelligence. Attention-deficit/hyperactivity disorder screening was done by a checklist of ADHD symptoms (Rösler, Retz-Junginger, Retz, & Stieglitz, 2008) and the WURS-k questionnaire (Retz-Junginger et al., 2002). None of the participants exceeded the cut-off score criterion in either of

Table 1
Cognitive and mental assessment.

	MPH (*n* = 13)		MOD (*n* = 12)		CAF (*n* = 14)		Total (*n* = 39)	
Mental Status								
ADHS-Checklist	2.0	(2.9)	3.8	(4.7)	4.2	(5.7)	3.4	(4.6)
BDI-V	12.5	(8.9)	14.3	(9.6)	11.9	(8.9)	12.8	(8.9)
WURS-K	12.3	(9.2)	13.2	(9.7)	12.3	(9.8)	12.6	(9.3)
Memory								
LGT-3 – verbal memory	43.1	(7.4)	43.7	(5.5)	45.4	(6.6)	44.1	(6.5)
LGT-3 – figural memory	31.5	(6.1)	30.5	(5.0)	31.2	(5.2)	31.1	(5.4)
LGT-3 – memory standard	88.3	(14.7)	88.8	(12.3)	92.0	(13.2)	89.8	(13.2)
numbers	18.9	(10.6)	14.9	(11.2)	12.6	(8.8)	14.4	(10.2)
Performance								
CFT-20R subtest 1	13.0	(1.9)	13.4	(0.9)	12.8	(1.9)	13.1	(1.6)
CFT-20R subtest 2	11.2	(1.9)	11.7	(1.0)	10.2	(2.5)	11.0	(2.0)
CFT-20R subtest 3	11.1	(2.4)	11.6	(2.0)	11.5	(2.1)	11.4	(2.1)
CFT-20R subtest 4	7.4	(1.4)	7.1	(2.2)	7.9	(1.4)	7.5	(1.7)
DSST	41.7	(6.9)	37.8	(9.9)	32.6	(16.6)	37.2	(12.4)
MWT	27.3	5.4	29.4	(2.8)	27.5	(4.1)	28.0	(4.3)

Results are mean (SD). No group differences in any score, all $p > .05$.

the two tests. Memory performance was measured using a learning and memory test (Bäumler, 1974). In addition, we tested short-term memory span using a long number that had to be recalled after an interval of 5 min ("numbers"). All subjects had physiological heart rate, blood pressure and did not show any abnormal ECG recordings. The study was approved by the local ethics committee (LAGeSo; 13/0138-EK12) and was conducted according to the codes of ethics on human experimentation (Declaration of Helsinki (1964) and the 2008 amendment). The study was registered at ClinicalTrials.gov (NCT02071615). Written informed consent was obtained from all participants.

2.2. Study design

The study had a double-blind, within-subject, placebo-controlled

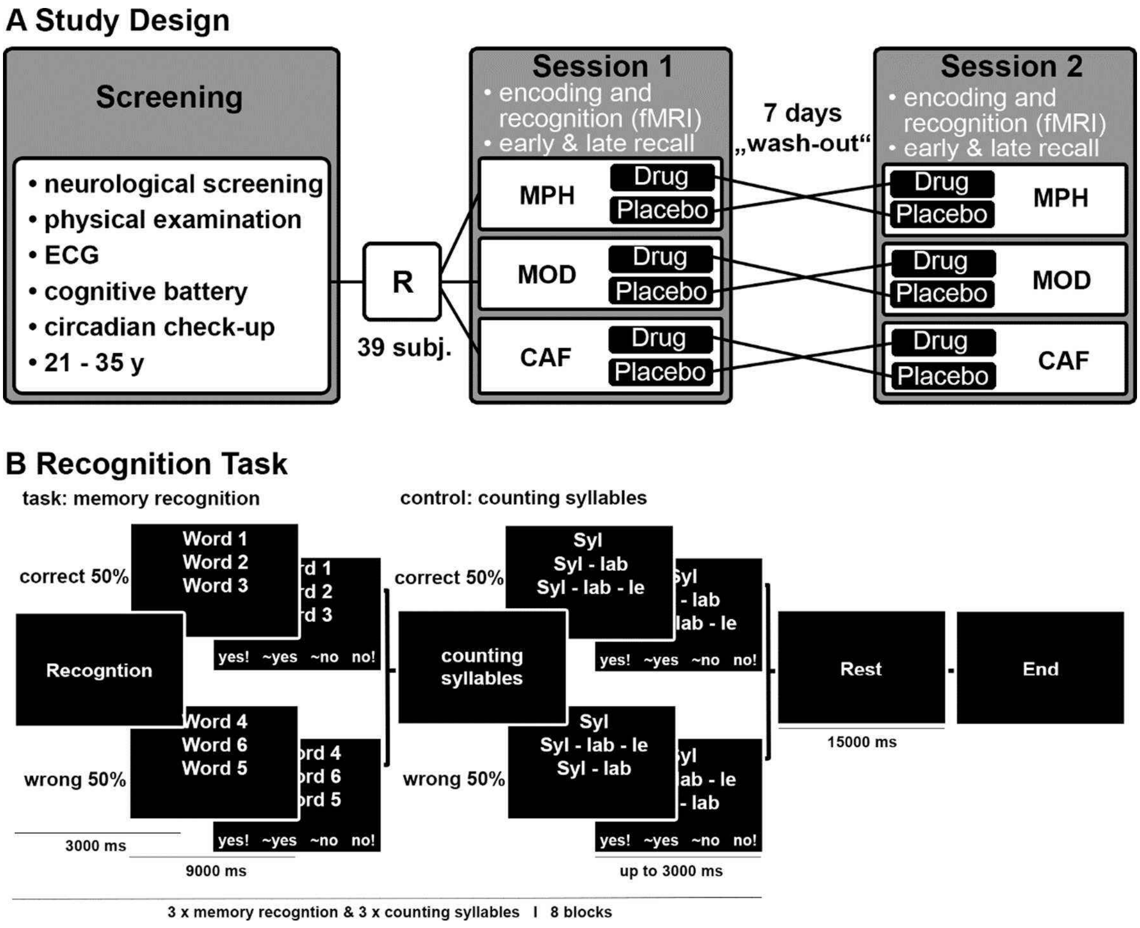

Fig. 1. Study design & task. (A) 39 participants started either with a placebo or one of the three substances MPH (n = 13), MOD (n = 12) or CAF (n = 14) in a double-blind fashion. In a second session after a 7 days wash-out period, the other substance or placebo was administered. In each session subjects performed an encoding and recognition task based on parallel word lists. (B) In the recognition task, participants had to judge the correct order of 24 word triplets that were previously learned during the encoding task. Word lists were presented for 9000 ms, whereas decision time was restricted to 3000 ms. After each block, a brief delay of 15 s gave subjects time to relax.

design. Participants were randomized to receive placebo and 20 mg MPH or 200 mg MOD or 200 mg CAF. Allocation to one of the three intervention arms was also double-blinded and each volunteer participated in only one intervention arm and received only one stimulant (Fig. 1A). Randomly starting with placebo or drug, participants were scanned twice, with in most cases seven days (and no less than four days) passing between the two sessions. To match the fMRI measurement period with the different peaks of maximal plasma concentrations ($C_{\max}$) of MPH, CAF and MOD, participants received the drugs orally 90 min prior to fMRI. Given an approximate time to reach $C_{\max}$ ($T_{\max}$) for CAF = 60 min, for MPH = 90–190 min, and MOD = 120 – 240 min, 90 min was chosen as a reasonable average to reach $T_{\max}$ of each substance (Dolder, Müller, Schmid, Borgwardt, & Liechti, 2017; Minzenberg & Carter, 2008; Swanson & Volkow, 2003; Volkow et al., 2015).

Heart rate and blood pressure was monitored regularly during the whole experimental procedure. To accustom to the scanning conditions, participants were set up in the scanner 15 min prior to functional imaging, while we acquired the localizer, the structural scan and a resting state scan. 24 h after each session participants were contacted via telephone to check their health status and collect late recall performance data on the declarative memory task that was running during fMRI data collection.

2.3. Imaging

Imaging was performed on a Siemens 3 T Magnetom Trio Scanner (Siemens Healthcare, Erlangen, Germany) using an echo planar protocol with a 12-channel head coil. Positioned head first and supine, participants received visual stimuli of the memory paradigm via video goggles (VisuaStimDigital, Resonance Technology Company Inc, CA, USA). Functional images were acquired in the axial plane using T2* weighted echo planar imaging (EPI) sequences (Time of Repetition (TR) = 2000 ms; Time of Echo (TE) = 30 ms, image matrix = 72x72, Field of View (FoV) = 216 mm, flip angle = 80°, slice thickness = 3 mm, distance factor = 20%, voxel size = 3x3x3 mm). Participants could independently pace their task responses during scanning, hence the time series vary in their number of volumes between trials and participants. For fMRI coregistration, 192 high-resolution T1 weighted 3D MPRAGE whole-brain sclices were recorded (TE = 4.77 ms, TR = 2500 ms, image matrix = 256x256, FoV = 256 mm, flip angle = 7°, slice thickness = 1 mm, voxel size = 1x1x1 mm).

2.4. Procedure

The memory task was tested and applied on mnemonic experts and healthy natives before and described in detail elsewhere (Dresler et al., 2017). Briefly, subjects had to learn and recognize the correct order of items of a word list. First, subjects had to learn 72 words subdivided in 12 blocks, as well as their order of appearance within each block ("encoding task"). Each block contained 6 words and lasted 40 s followed by 25 s of resting. All random German words appeared in white font on black background. On each test session, different word lists were used.

Immediately after the learning task, a recognition task followed in the scanner in order to measure declarative memory retrieval ("recognition task", Fig. 1B). During eight blocks of randomized order, a total of 24 recognition and 24 control trials were run by all subjects. Thereby, triplets of words from the learned word list were presented and participants had to indicate whether the same order of words was previously presented during the encoding task. This included the acceptance of a correct order as well as the rejection of a wrong order. To correct for any bias of very slow responses that were not recorded due to the response window of 3000 ms, all data was corrected for response misses. As a control condition, triplets of new words were presented and participants were asked to count the syllables of presented words and decide about the ascending (or not) number of word syllables

To further assess recall performance, participants were asked to recall as many words of the learning task as possible immediately after scanning ("early recall"). As previously described by Dresler et al. (2017), all participants were contacted 24 h later, and asked to recall all words of the learning task again ("late recall") (Dresler et al., 2017). Commission errors, i.e. items that were not part of the word list, were not counted.

Data from six participants had to be excluded from the memory task analysis due to technical problems (3 in MPH, 2 in MOD and 1 in CAF). Furthermore, two participants of the MOD and one participant of the CAF group have been dismissed from imaging analysis due to head movements that exceeded 3 mm. In total, complete behavioral and imaging data were collected for 39 participants (MPH = 13, MOD = 12, CAF = 14).

2.5. Data analysis

For behavioral data, SPSS (SPSS® Statistics 22.0) was used. Behavioral measures were analyzed separately using repeated-measures analysis of variance (ANOVA) to isolate the treatment effect. To analyze the recognition task, a repeated-measures ANOVA with the within-subject factor treatment (drug/placebo) and the between-subject factor drug type (MPH/MOD/CAF) was performed to assess recognition performance. To explore a treatment effect on confidence ratings, an analysis of covariance (ANCOVA) with task performance as a covariate was performed. Number of correct recognition responses and percentage of high confidence responses were set as dependent variables. To assess early and late recall, a repeated-measures ANOVA was performed with the between-subject factor drug type (MPH/MOD/CAF) and the within-subject factors time (early/late recall) and treatment effect (drug/placebo). The number of freely recalled words was used as the dependent variable. Subsequently, Wilcoxon rank test was used for comparison between drug and placebo scores of each group.

Imaging data was analyzed with Statistical Parametric Mapping 12 (SPM12, Wellcome Trust Centre for Neuroimaging), a toolbox running in MathWorks MATLAB (https://de.mathworks.com/products/matlab.html). First, all images of each subject were corrected for slice timing and realignment. In the next step, a mean functional EPI image was constructed from the realigned EPI images for each subject. This image was co-registered with a T1 MPRAGE anatomical image. Furthermore, preprocessing included segmentation and spatial normalization to the Montreal Neurological Institute space (MNI). For normalization, a unified segmentation was used to classify anatomical T1-weighted images into gray matter, white matter, and cerebrospinal fluid (Ashburner & Friston, 2005). Finally, data were smoothed with a 6 mm FWHM Gaussian kernel (full-width at half maximum). The fMRI time series data were high-pass filtered (cutoff, 128 s).

Statistics were performed using the general linear model (GLM) approach. At the first level, a GLM was created using regressors at the onset of stimulus presentation and responses for the encoding and recognition task, respectively. Additionally, movement parameters as regressors of no interest were included in the model. For encoding, the contrasts between learning and rest (Learning > Resting; Resting > Learning) were computed, with word list items recorded as events, whereas the resting condition consisted of blocks of 25 s duration.

The following were selected as the main regressors of interest for the recognition task: (1) correct task response under drug, (2) correct control response under drug, (3) correct task response under placebo, (4) correct control response under placebo. In the first level analysis of the recognition task, neural activity during correctly processed task items were contrasted to items that were correctly processed during the control condition (Recognition > Control; Control > Recognition). On the second level, contrast maps of the single-subject analyses were used to contrast drug with placebo effects within the encoding and the recognition task. Main contrasts of interest for encoding and recognition were computed over all 39 participants and separately for each stimulant alone. Unless otherwise indicated, statistical values of the whole brain analysis were thresholded at a significance level of $p < .001$. Data was corrected for multiple comparisons based on 10,000 Monte Carlo simulations. A significant effect corresponding a type I alpha error probability of $p < .05$ was assumed when the volume exceeded the minimum cluster size that was computed for each second level contrast (3dClustSim, AFNI version 17.01.03) (Cox, 1996). FWHM smoothness estimates are based on first level individual subject data. MNI coordinates of activated areas were assigned to brain regions using the SPM function “Neuromorphometrics” as well as the Anatomy toolbox (Eickhoff et al., 2005) and WFU Pickatlas (Tzourio-Mazoyer et al., 2002).

Regions revealing significant effects of certain drugs were correlated with behavioral measures as well as individual, body-weight adapted drug dose. Using the SPM VOI function, activation values of activated regions on the whole brain level were extracted from spherical masks with a radius of 10 mm around the peak coordinates.

3. Results

3.1. Behavioral data

For the recognition task, no treatment effect on task performance was found ($F(1, 39) = 0.09$, $p > .77$). Also, there was no treatment effect on confidence ratings after controlling for task performance ($p > 0.11$). Confidence ratings in the control task responses were used as a control of motivation and effort. Here, all participants had a performance above 90% correct trials.

3.2. Imaging data

3.2.1. Encoding

During encoding, there was no significant main effect of each drug vs. placebo found on blood-oxygen-level dependent (BOLD) response signal for Learning > Resting or Resting > Learning. MPH and MOD neither activated nor deactivated BOLD signal in any brain region during any interaction ($p > .05$). However, in the CAF group the contrast (Placebo(Learning > Resting) > Drug(Learning > Resting)) showed enhanced BOLD signal bilaterally in the precentral gyrus, medium segment (peak voxel: 0, −31, 62, $t(13) = 5.53$, $p < .05$, cluster size of 24 voxels, Brodmann area BA4). Furthermore, the same region (peak voxel: 0, −31, 62, $t(13) = 6.5$, $p < .05$, cluster size of 50 voxels, BA4) together with another cluster in the left insula/parietal operculum (peak voxel: −51, −10, 20, $t(13) = 6.33$, cluster size of 35 voxels, BA40) were deactivated in the interaction contrast Learning X CAF (CAF (Learning > Resting)>(Placebo > Drug)) (Table 2).

None of the deactivated regions showed any significant correlation to behavioral performance measures.

Table 2
Peak Voxels of task-drug-interactions.

Region	BA	MNI coordinates			Laterality	*t*-score	*k*
		X	Y	Z			
Deactivations Learning X CAF[1]							
Precentral gyrus	4	0	−31	62	R/L	6.50	50
Parietal operculum	40	−51	−10	20	L	6.33	35
Deactivations Recognition X MPH[2]							
SMA	6	−6	−16	68	R/L	7.58	45
Superior temporal gyrus	41	48	−34	14	R	7.44	27
Lingual Gyrus	18	−9	−73	−7	L	6.43	24

BA = Brodmann’s area. The minimum cluster size to correct for multiple comparisons was determined by Monte Carlo simulations ($p < .001$; 3dClustSim), (1) N = 14, FWHM 8.7394 8.6916 8.3495, two-tailed, $k > 23$. (2) N = 13, FWHM 8.6527 8.6019 8.3870, two-tailed, $k > 23$.

3.2.2. Recognition

In the MPH group, there was a significant Recognition X MPH interaction (MPH(Recognition > Control)>(Placebo > Drug)). Deactivations were found in supplementary motor area (SMA), right middle temporal gyrus, and left lingual gyrus (Table 2; Fig. 2A). No increased BOLD signal was found for the interaction Recognition X MPH. Due to its relative value, an interaction contrast cannot be taken as an absolute indication for a certain BOLD shift, i.e. a deactivation caused by MPH. To examine the interaction effects, the biggest cluster, SMA (-6, −16, 68), was further investigated as an example. First, a ROI was created on the basis of activated voxels. The beta weights of the ROI SMA were extracted for recognition as well as for the control condition (Fig. 2B). During the control condition, voxels within the ROI appeared to be more strongly activated than during recognition task, but there was no significant difference, $p > .09$ (Fig. 2C). Second, the contrasts of the Recognition X MPH interaction in particular were examined. For this purpose, the beta weights of the single contrasts MPH_Recognition > Baseline, MPH_Control > Baseline, Placebo_Recognition > Baseline, Placebo_Control > Baseline were extracted for the ROI SMA. Further, the interaction of the two factors treatment (MPH vs. placebo) and task (recognition vs. control) was calculated ($F_{(1,48)} = 10.29$, $p < .01$). This revealed a bidirectional effect of the factor task during MPH but not during placebo (Fig. 2D). Hence, the basis of the interaction contrast Recognition X MPH is formed by either an increase of BOLD signal during control condition or a decrease during the recognition task. A whole-brain analysis of the interaction between Recognition and CAF and MOD respectively, did not show any significant clusters.

The deactivated areas of the MPH group during task assessment did not show any relationships to recognition performance or early and late recall. However, the VOI analysis of the left lingual gyrus ($r = 0.61$) and the right superior temporal gyrus ($r = 0.76$) revealed a correlation with the applied MPH dose/ kg body weight. No such significant correlations were found for the SMA region or the left occipital gyrus. The contrast estimates did not correlate with any cognitive or behavioral score. Control analyses of learning and recognition effects of all subjects can be found in the supplemental data.

4. Discussion

In this study, the influence of methylphenidate, modafinil, and caffeine on declarative memory function was investigated in healthy adults using fMRI. At the neural level, CAF was found to decrease activation in the precentral gyrus during encoding, whereas both other drugs did not show any effect here. During recognition of a word sequence, MPH led to decreases in BOLD signal in the SMA as well as small clusters in the temporo-occipital region. No effect was found for MOD or CAF. Behavioral results are reported elsewhere (Repantis et al., 2021). Briefly, after MPH intake, subjects’ recognition and early recall performance of a previously learned word list was comparable to the placebo condition. However, consistent with previous studies, MPH enhanced performance in late recall (Kuypers & Ramaekers, 2005; Linssen, Vuurman, Sambeth, & Riedel, 2012). Cardiovascular data remained within physiological range in all participants during the study period. Twelve mild adverse events such as transient headaches and sleep disturbances were reported in total while no severe adverse event was apparent.

4.1. Methylphenidate

To investigate neural changes after MPH intake, an interaction analysis of drug and task was conducted. While no difference between MPH and placebo was seen during encoding, there was a significant decrease in signal in the SMA, temporal, occipital, and lingual gyri during recognition. These deactivations do not necessarily imply lower performance. Instead, such deactivations are well known in the literature as task-induced deactivations that may reflect a reallocation of

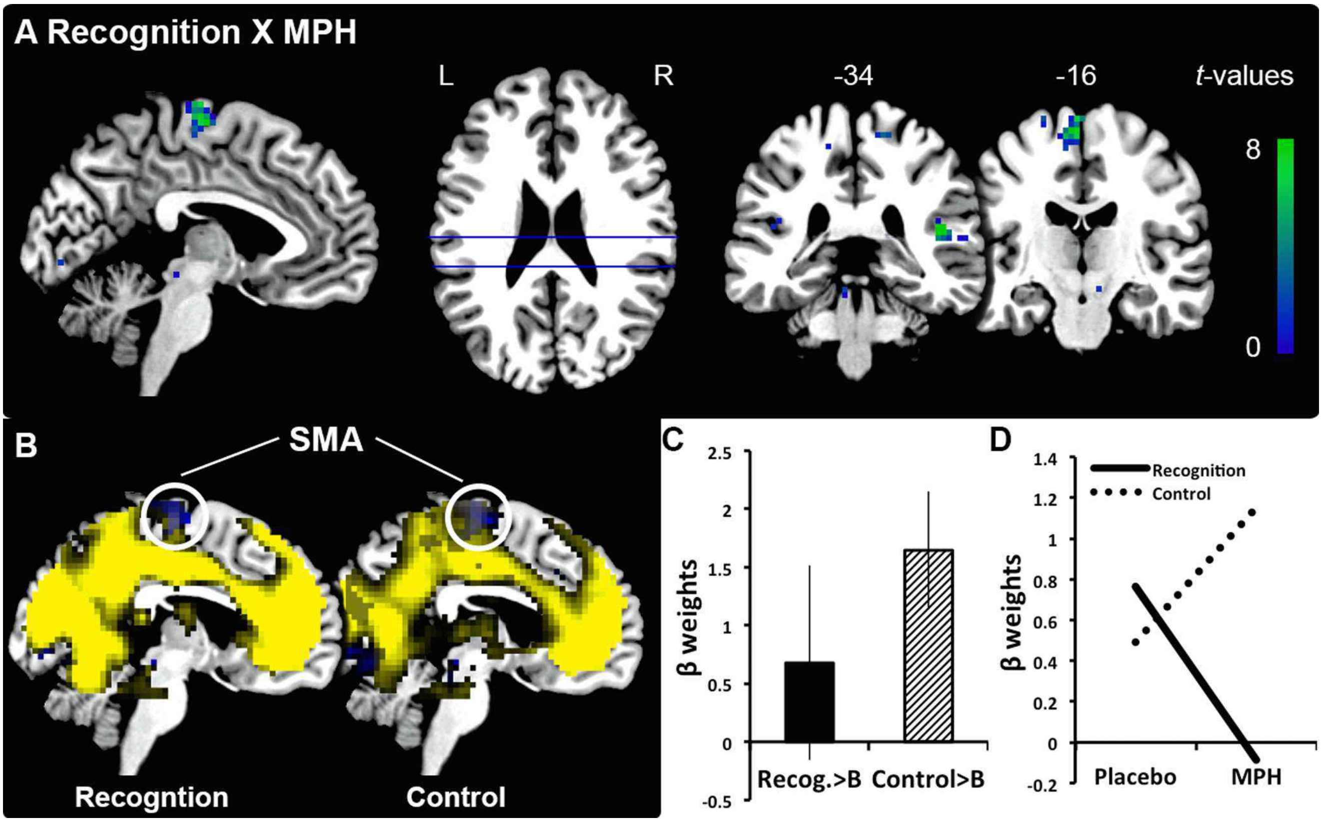

Fig. 2. Results of the interaction for Recognition X MPH. (A) Task and MPH-dependent signal deactivations. (B) Overlap of the ROI SMA (blue) and activated regions for the contrasts Recognition > Baseline and Control > Baseline (yellow). (C) Comparison of grouped beta weights for the contrasts Recognition > Baseline and Control > Baseline, difference is not significant, p > .05. (D) Plotted interaction of the extracted beta weights of the factors task and MPH treatment (D), B = Baseline. L = left, R = right. All clusters > 23 voxels are shown. The minimum cluster size to correct for multiple comparisons was determined by Monte Carlo simulations (p < .001; 3dClustSim). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

neurocognitive resources (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003). Task-induced deactivations were previously linked to different beneficial states of cognitive qualities, including encoding processes (Daselaar, Prince, & Cabeza, 2004) and working memory (Tomasi et al., 2011).

Among the areas showing decreased signal, the SMA represents the largest cluster. The SMA is located in the superior and medial part of the superior frontal gyrus, adjacent to the primary motor cortex. With its projections to the spinal cord (He, Dum, & Strick, 1993) and primary motor cortex (Luppino, Matelli, Camarda, & Rizzolatti, 1993), the SMA is typically associated with the control and preparation of voluntary motor functions (Nachev, Kennard, & Husain, 2008). In addition, multiple white matter strings connect the SMA to striatal cores and language associated regions, suggesting a role that is not restricted to the domain of motor control, i.e. higher cognitive functions and speech production (Alario, Chainay, Lehericy, & Cohen, 2006; Lehericy et al., 2004).

The contribution of the SMA in semantic memory is less clear. In line with our results, several previous studies emphasized a role of the SMA in memory retrieval (Gotts, Milleville, Bellgowan, & Martin, 2011; Grossman et al., 2002; Hart et al., 2013). Hart and colleagues proposed a functional–anatomic organization of modality-specific semantic memory system (Hart et al., 2013). The authors proposed a SMA-thalamic circuit that is engaged in complex, controlled semantic search and retrieval. Thereby, the SMA initiates the process of alignment of new object to memorized chunks. The retrieval of correct matches is represented by changes in high beta band EEG power in (pre-)SMA, thalamus, and parieto-occipital cortical regions. In contrast to Hart et al. (2013) we used a different paradigm to assess correct memory retrieval of stored memory representations. However, Dresler et al. (2017) showed, that the study paradigm could reliably assess encoding and retrieval, even in mnemonic athletes (Dresler et al., 2017).

While it is known that premotor regions contain projections of dopamine releasing neurons (Garraux, Peigneux, Carson, & Hallett, 2007), the role of MPH in modulating SMA activity during semantic memory retrieval is not yet understood. Given the involvement of the SMA in semantic memory retrieval and elevated dopamine release by MPH, the administration of MPH could have yielded to a reduced use of attentional resources in this region during memory retrieval. Drug-naïve subjects performing a mathematical calculation task showed a similar pattern of MPH-dependent attenuation of brain metabolic increases during the task, but not during resting. This might have led to a reduced use of attentional resources in the human brain that are necessary to achieve similar levels of performance (Volkow et al., 2008). Overall, this evidence suggests that the dopamine-mediated neurons within the SMA may play an important role in the modulation of memory retrieval and that MPH lead to a more efficient memory recognition.

Given the interaction effect of task (word order recognition vs. counting syllables) and MPH-induced activity alteration in the SMA, it is noteworthy to consider the reasons for the increased activation within the SMA during the control task as well. Associated with endogenous dopamine release (Simonyan, Herscovitch, & Horwitz, 2013), the SMA involvement in linguistic processing is subject of a current neuroscientific debate (Pavlova et al., 2019), for review see Hertrich et al. (2016) (Hertrich, Dietrich, & Ackermann, 2016). It is hypothesized that encoding and decoding of language is processed in neural networks overlapping with those that are fundamental for action processing (Cappa & Pulvermuller, 2012). First of all, evidence for SMA involvement in language processing was seen in a variety of lesion studies. It is long known that patients suffering from SMA damages deal with movement restrictions, i.e. hemiparesis, and speech-related symptoms simultaneously (Chivukula, Pikul, Black, Pouratian, & Bookheimer, 2018; Krainik et al., 2003; Ziegler, 1997). According to a traditional view, language processing is mainly mediated by the posterior temporal lobe of the left hemisphere, BA44 (Geschwind, 1970). However, as neuroscientific techniques advanced, several other distinct brain regions, including pre-SMA and SMA, were found to be critical for language comprehension (Price, 2010; Turken & Dronkers, 2011). Chivukula and colleagues (2018) were not only able to illustrate multiple speech deficits after tumor resection in the SMA region, but showed by fMRI the remodeling of the neural network to the contralateral SMA after full recovery several months later.

MPH therefore seems to activate voxels in the SMA area during lexical processing while it decreases activation during retrieval at the same time (see Fig. 2). This task dependency is consistent with previous data showing that different cognitive requirements lead to different signal alterations under MPH in the same patient group (Clatworthy et al., 2009; Dodds et al., 2008).

Another significant cluster of deactivated voxels during recognition was found within the superior temporal gyrus, an area that was previously linked to (auditory) temporal information (Bueti, van Dongen, & Walsh, 2008). Simultaneous reduction in activity in SMA and temporal gyri may reveal an increased efficacy in the correct retrieval of temporal order. In contrast to these suspected efficacy enhancements, no task performance improvement was seen in subjects during MPH intake. Previous studies on MPH and other dopaminergic drugs have also suggested that reductions in cerebral blood flow not accompanied by better behavioral performance reflect an increased efficiency of task-related networks (Magalona et al., 2013; Mehta et al., 2000; Pauls et al., 2012).

An alternative underlying mechanism of action of MPH may be an enhanced task-related processing with simultaneous reduction in distractibility (Volkow et al., 2001). This was also argued in a study that found deactivations within the BA23 and BA31 during a working memory task after MPH intake (Tomasi et al., 2011). The claim of an MPH-mediated increase in filtering may also be true for other dopamine sensitive areas such as the SMA. The increase in dopamine through MPH leads to a decreased activation in selective parts of the brain that altogether increase the signal-to-noise ratio in attentional processes and thus eventually lead to better performance.

4.2. *Modafinil*

Our data are in line with the results of a *meta*-analysis (Repantis et al., 2010) where likewise no positive memory effects of MOD in studies with non-sleep-deprived participants were reported. We could not identify any task-related effect on the neural level. This is in contrast to other studies, i.e. Schmidt et al. (2017) who found activations in the right middle frontal gyrus and superior/inferior parietal lobule during a response inhibition task (Schmidt et al., 2017). However, the absence of MOD effects on the neural level has been reported in other studies as well (Schmaal et al., 2014; Schmaal et al., 2013), suggesting a dose- and task-dependent enhancement effect. Future studies should address in more detail why MOD presumably acts on response inhibition and working memory but not on declarative memory processing.

4.3. *Caffeine*

CAF did not alter memory performance in the recognition task or during recalling the learned word list, a result that is also supported by the literature. In the CAF condition the recognition task did not induce any signal alterations, whereas during the encoding phase there were deactivations bilateral in the precentral gyrus as well as in the left parietal operculum. This distinct anatomic region represents the human primary motor cortex. The identified cluster corresponds to an area that usually reflects movements of the feet (Meier, Aflalo, Kastner, & Graziano, 2008). However, in the literature the motor cortex is linked also to processes that go beyond the mere initiation of movement. For instance, precentral activity is assumed to mediate learning and memory of motor sequences (Sanes, 2000) as well as verbal processing (Shergill et al., 2001). Furthermore, there is support for the hypothesis that medial and lateral precentral areas are involved in reading and word repetition (Alario et al., 2006). Nevertheless, a deactivation in the medial precentral gyrus that corresponds to certain cognitive phenomena has not been reported so far in the literature. Since the precentral gyrus is functionally closely connected to the SMA (Halsband & Lange, 2006), it can be speculated that CAF induces a mechanism similar to that of MPH during recognition. The other cluster of deactivated voxels most likely corresponds to the most ventral part of the precentral gyrus and area IV, which is the dorso-lateral part of the operculum. Besides its proposed main function of sensory-motor integration (Wasaka et al., 2005), the authors of another study reported functional importance of the operculum for sensory sequence learning (Romo, Hernandez, Zainos, Lemus, & Brody, 2002). Besides motor tasks, the operculum seems to be also responsible for general verbal processing (A. D. Wagner et al., 1998). Abel and colleagues (2012) also found deactivations within the parietal operculum when participants performed a lexical task (Abel, Dressel, Weiller, & Huber, 2012). Deactivations in sensory areas during lexical priming were proposed to be responsible for an increase in efficacy. Eventually this also holds for learning processes. CAF's effect on brain function was the subject of research in numerous previous studies, however, most of the imaging studies either examined CAF function in resting state (Wu, Lien, Chang, & Yang, 2014) or its effect in sensory perception (Laurienti et al., 2002; Liu et al., 2004). Despite difficulties in CAF-dependent neural assessment, a few studies examined working memory processes under the influence of CAF in younger (Klaassen et al., 2013; Koppelstaetter et al., 2008) and older participants (Haller et al., 2014; Haller et al., 2013). Compared to these working memory studies, we did not detect any activation in prefrontal or cingulate areas. Koppelstaetter and colleagues (2008) let participants perform an n-back task after CAF or placebo administration (Koppelstaetter et al., 2008). Though applying half the dose of our study, the task-drug interaction in their study revealed activations in the medial frontopolar cortex (BA10) as well as parts of the anterior cingulate cortex (BA32). In the study by Klaassen and colleagues (2013), participants under the influence of CAF or placebo performed a Sternberg task within the scanner. Similar to Koppelstaetter and colleagues (2008), the drug-task-interaction pointed towards an increased signal within the PFC during encoding. Those areas are usually associated with planning and reasoning (Braver & Bongiolatti, 2002), but not necessarily with encoding or recall, which was the main focus in our study. Besides neural activation changes, CAF-induced vasoactive alterations have also been shown in the past (Laurienti et al., 2003). So far, it is not clear if these two effects interact with each other or occur independently (Koppelstaetter et al., 2010). In any case, task-related neural activity patterns in patients under CAF need to be interpreted with caution.

4.4. *Limitations*

Several limitations of this study need to be acknowledged and addressed in the future. First, since this was a pilot study no power calculation was performed and the number of participants in each of the intervention arms was quite small. Even though functional MRI studies usually deal with small numbers of participants, this runs the risk of overlooking weak drug effects that may have altered the participant's performance. We may have missed brain-behavior correlations due to low statistical power. Moreover, although we did not find significant negative effects of any of the drugs on healthy individuals in this pilot study, potential side effects may only become apparent in a larger sample.

Second, we did not control for individual drug plasma concentration after application of each substance. However, this should be considered in future studies since it is known that deviations from the effective drug level may reduce the positive enhancement effect or even cause harm and performance drop (Cools & D'Esposito, 2011). Although we did not record any severe adverse effects or impairment in any of the assessments in our test battery, potential negative consequences caused by cognitive enhancement, i.e. by competitive neural and cognitive resources, should be carefully monitored in subsequent studies (Colzato, Hommel, & Beste, 2021). A further methodological limitation is the lack of control for vasoactive properties of the investigated drugs, most notably of caffeine.

5. Conclusions

If subsequent studies with a larger sample size corroborate our findings, our pilot study may have important implications for the understanding of the modulation of the memory system of healthy adults. Our findings indicate that a single dose of MPH deactivates signal within several brain regions that may reflect an increase in efficacy in data processing. While we report distinct effects for MPH and CAF, no effect could be found for MOD. Further studies are needed to clarify the effect of memory-affecting drug agents and inform a richer model of human memory function.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by a grant (No. 85648) of the Volkswagen Foundation, Germany. The Volkswagen Foundation had no role in the design, data collection, data analysis, data interpretation, or writing of the manuscript. SK has been funded by two grants from the German Science Foundation (DFG KU 3322/1-1, SFB 936/C7), the European Research Council (ERC-2016-StG-Self-Control-677804) and a Fellowship from the Jacobs Foundation (JRF 2016-2018).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bandc.2021.105802.

References

Abel, S., Dressel, K., Weiller, C., & Huber, W. (2012). Enhancement and suppression in a lexical interference fMRI-paradigm. *Brain Behavior, 2*(2), 109–127.

Alario, F.-X., Chainay, H., Lehericy, S., & Cohen, L. (2006). The role of the supplementary motor area (SMA) in word production. *Brain Research, 1076*(1), 129–143.

Andrzejewski, M. E., Spencer, R. C., Harris, R. L., Feit, E. C., McKee, B. L., & Berridge, C. W. (2014). The effects of clinically relevant doses of amphetamine and methylphenidate on signal detection and DRL in rats. *Neuropharmacology, 79*, 634–641.

Arnsten, A. F., & Dudley, A. G. (2005). Methylphenidate improves prefrontal cortical cognitive function through alpha2 adrenoceptor and dopamine D1 receptor actions: Relevance to therapeutic effects in Attention Deficit Hyperactivity Disorder. *Behavioral and Brain Functions, 1*(1), 2.

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *Neuroimage, 26*(3), 839–851.

Baranski, J. V., Pigeau, R., Dinich, P., & Jacobs, I. (2004). Effects of modafinil on cognitive and meta-cognitive performance. *Human Psychopharmacology: Clinical and Experimental, 19*(5), 323–332.

Battleday, R. M., & Brem, A.-K. (2015). Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: A systematic review. *Eur Neuropsychopharmacology, 25*(11), 1865–1881.

Bäumler, G. (1974). *Lern-und Gedächtnistest.* LGT-3: Hogrefe.

Berridge, C. W., Devilbiss, D. M., Andrzejewski, M. E., Arnsten, A. F. T., Kelley, A. E., Schmeichel, B., et al. (2006). Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biological Psychiatry, 60*(10), 1111–1120.

Borota, D., Murray, E., Keceli, G., Chang, A., Watabe, J. M., Ly, M., et al. (2014). Post-study caffeine administration enhances memory consolidation in humans. *Nature Neuroscience, 17*(2), 201–203.

Borst, J. P., & Anderson, J. R. (2013). Using model-based functional MRI to locate working memory updates and declarative memory retrievals in the fronto-parietal network. *Proceedings of the National Academy Sciences of the United States of America, 110*(5), 1628–1633.

Braver, T. S., & Bongiolatti, S. R. (2002). The role of frontopolar cortex in subgoal processing during working memory. *Neuroimage, 15*(3), 523–536.

Bueti, D., van Dongen, E. V., Walsh, V., & Greene, E. (2008). The role of superior temporal cortex in auditory timing. *Public Library of Science One, 3*(6), e2481.

Cappa, S. F., & Pulvermüller, F. (2012). Cortex special issue: Language and the motor system. *Cortex, 48*(7), 785–787.

Carmack, S. A., Block, C. L., Howell, K. K., & Anagnostaras, S. G. (2014). Methylphenidate enhances acquisition and retention of spatial memory. *Neuroscience Letter, 567*, 45–50.

Chivukula, S., Pikul, B. K., Black, K. L., Pouratian, N., & Bookheimer, S. Y. (2018). Contralateral functional reorganization of the speech supplementary motor area following neurosurgical tumor resection. *Brain Language, 183*, 41–46.

Clatworthy, P. L., Lewis, S. J. G., Brichard, L., Hong, Y. T., Izquierdo, D., Clark, L., et al. (2009). Dopamine release in dissociable striatal subregions predicts the different effects of oral methylphenidate on reversal learning and spatial working memory. *Journal of Neuroscience, 29*(15), 4690–4696.

Colzato, L. S., Hommel, B., & Beste, C. (2021). The Downsides of Cognitive Enhancement. *Neuroscientist, 27*(4), 322–330.

Compton, W. M., Han, B., Blanco, C., Johnson, K., & Jones, C. M. (2018). Prevalence and Correlates of Prescription Stimulant Use, Misuse, Use Disorders, and Motivations for Misuse Among Adults in the United States. *The American Journal of Psychiatry, 175*(8), 741–755.

Cools, R., & D'Esposito, M. (2011). Inverted-U-shaped dopamine actions on human working memory and cognitive control. *Biological Psychiatry, 69*(12), e113–e125.

Cox, R. W. (1996). AFNI: Software for Analysis and Visualization of Functional Magnetic Resonance Neuroimages. *Computers and Biomedical Research, 29*(3), 162–173.

Daselaar, S. M., Prince, S. E., & Cabeza, R. (2004). When less means more: Deactivations during encoding that predict subsequent memory. *Neuroimage, 23*(3), 921–927.

Dauvilliers, Y., Billiard, M., & Montplaisir, J. (2003). Clinical aspects and pathophysiology of narcolepsy. *Clinical Neurophysiology, 114*(11), 2000–2017.

de Jongh, R., Bolt, I., Schermer, M., & Olivier, B. (2008). Botox for the brain: Enhancement of cognition, mood and pro-social behavior and blunting of unwanted memories. *Neuroscience & Biobehavioral Reviews, 32*(4), 760–776.

del Campo, N., Fryer, T. D., Hong, Y. T., Smith, R., Brichard, L., Acosta-Cabronero, J., et al. (2013). A positron emission tomography study of nigro-striatal dopaminergic mechanisms underlying attention: implications for ADHD and its treatment. *Brain, 136*(Pt 11), 3252–3270.

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. *Journal of Neuroscience, 28*(23), 5976–5982.

Dolder, P. C., Müller, F., Schmid, Y., Borgwardt, S. J., & Liechti, M. E. (2018). Direct comparison of the acute subjective, emotional, autonomic, and endocrine effects of MDMA, methylphenidate, and modafinil in healthy subjects. *Psychopharmacology (Berl), 235*(2), 467–479.

Dresler, M., Shirer, W. R., Konrad, B. N., Müller, N. C. J., Wagner, I. C., Fernández, G., et al. (2017). Mnemonic Training Reshapes Brain Networks to Support Superior Memory. *Neuron, 93*(5), 1227–1235.e6.

Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., et al. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage, 25*(4), 1325–1335.

Elliott, R., Sahakian, B. J., Matthews, K., Bannerjea, A., Rimmer, J., & Robbins, T. W. (1997). Effects of methylphenidate on spatial working memory and planning in healthy young adults. *Psychopharmacology (Berl), 131*(2), 196–206.

Ferré, S. (2016). Mechanisms of the psychostimulant effects of caffeine: Implications for substance use disorders. *Psychopharmacology (Berl), 233*(10), 1963–1979.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy Sciences of the United States of America, 102*(27), 9673–9678.

Garraux, G., Peigneux, P., Carson, R. E., & Hallett, M. (2007). Task-related interaction between basal ganglia and cortical dopamine release. *Journal of Neuroscience, 27*(52), 14434–14441.

Geschwind, N. (1970). The organization of language and the brain. *Science, 170*(3961), 940–944.

Goldman-Rakic, P. S. (1995). Cellular basis of working memory. *Neuron, 14*(3), 477–485.

Gotts, S. J., Milleville, S. C., Bellgowan, P. S., & Martin, A. (2011). Broad and narrow conceptual tuning in the human frontal lobes. *Cerebral Cortex, 21*(2), 477–491.

Grossman, M., Smith, E. E., Koenig, P., Glosser, G., DeVita, C., Moore, P., et al. (2002). The neural basis for categorization in semantic memory. *Neuroimage, 17*(3), 1549–1561.

Haller, S., Montandon, M.-L., Rodriguez, C., Moser, D., Toma, S., Hofmeister, J., et al. (2014). Acute caffeine administration effect on brain activation patterns in mild cognitive impairment. *Journal of Alzheimer's Disease, 41*(1), 101–112.

Haller, S., Rodriguez, C., Moser, D., Toma, S., Hofmeister, J., Sinanaj, I., et al. (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.

Halsband, U., & Lange, R. K. (2006). Motor learning in man: A review of functional and clinical studies. *Journal of Physiology Paris, 99*(4-6), 414–424.

Hameleers, P. A. H. M., Van Boxtel, M. P. J., Hogervorst, E., Riedel, W. J., Houx, P. J., Buntinx, F., et al. (2000). Habitual caffeine consumption and its relation to memory, attention, planning capacity and psychomotor performance across multiple age groups. *Human Psychopharmacology: Clinical and Experimental, 15*(8), 573–581.

Hart, J., Maguire, M. J., Motes, M., Mudar, R. A., Chiang, H.-S., Womack, K. B., et al. (2013). Semantic memory retrieval circuit: Role of pre-SMA, caudate, and thalamus. *Brain Language, 126*(1), 89–98.

He, S. Q., Dum, R. P., & Strick, P. L. (1993). Topographic organization of corticospinal projections from the frontal lobe: Motor areas on the lateral surface of the hemisphere. *Journal of Neuroscience, 13*(3), 952–980.

Hermens, D. F., Cooper, N. J., Clark, C. R., Debrota, D., Clarke, S. D., & Williams, L. M. (2007). An integrative approach to determine the best behavioral and biological markers of methylphenidate. *Journal of Integrative Neuroscience, 6*(1), 105–140.

Hertrich, I., Dietrich, S., & Ackermann, H. (2016). The role of the supplementary motor area for speech and language processing. *Neuroscience & Biobehavioral Review, 68*, 602–610.

Kensinger, E. A., & Corkin, S. (2003). Memory enhancement for emotional words: Are emotional words more vividly remembered than neutral words? *Memory & Cognition, 31*(8), 1169–1180.

Klaassen, E. B., de Groot, R. H. M., Evers, E. A. T., Snel, J., Veerman, E. C. I., Ligtenberg, A. J. M., et al. (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., Kolbitsch, C., Mottaghy, F. M., et al. (2010). Caffeine and cognition in functional magnetic resonance imaging. *Journal of Alzheimer's Disease, 20*(s1), S71–S84.

Koppelstaetter, F., Poeppel, T. D., Siedentopf, C. M., Ischebeck, A., Verius, M., Haala, I., et al. (2008). Does caffeine modulate verbal working memory processes? *An fMRI study. Neuroimage, 39*(1), 492–499.

Krainik, A., Lehéricy, S., Duffau, H., Capelle, L., Chainay, H., Cornu, P., et al. (2003). Postoperative speech disorder after medial frontal surgery: Role of the supplementary motor area. *Neurology, 60*(4), 587–594.

Kuypers, K. P. C., & Ramaekers, J. G. (2005). Transient memory impairment after acute dose of 75mg 3.4-Methylene-dioxymethamphetamine. *Journal of Psychopharmacology, 19*(6), 633–639.

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*(2), 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. *American Journal of Neuroradiology, 24*(8), 1607–1611.

Lehericy, S., Ducros, M., Krainik, A., Francois, C., Van de Moortele, P. F., Ugurbil, K., et al. (2004). 3-D diffusion tensor axonal tracking shows distinct SMA and pre-SMA projections to the human striatum. *Cerebral Cortex, 14*(12), 1302–1309.

Lehrl, S. (1999). *Mehrfachwahl-Wortschatz-Intelligenztest: MWT-B*. Spitta.

Linssen, A. M. W., Sambeth, A., Vuurman, E. F. P. M., & Riedel, W. J. (2014). Cognitive effects of methylphenidate and levodopa in healthy volunteers. *Journal of the European Neuropsychopharmacology, 24*(2), 200–206.

Linssen, A. M. W., Vuurman, E. F. P. M., Sambeth, A., & Riedel, W. J. (2012). Methylphenidate produces selective enhancement of declarative memory consolidation in healthy volunteers. *Psychopharmacology (Berl), 221*(4), 611–619.

Lisman, J. E., & Grace, A. A. (2005). The hippocampal-VTA loop: Controlling the entry of information into long-term memory. *Neuron, 46*(5), 703–713.

Lisofsky, N., Mårtensson, J., Eckert, A., Lindenberger, U., Gallinat, J., & Kühn, S. (2015). Hippocampal volume and functional connectivity changes during the female menstrual cycle. *Neuroimage, 118*, 154–162.

Liu, T. T., Behzadi, Y., Restom, K., Uludag, K., Lu, K., Buracas, G. T., et al. (2004). Caffeine alters the temporal dynamics of the visual BOLD response. *Neuroimage, 23* (4), 1402–1413.

Luppino, G., Matelli, M., Camarda, R., & Rizzolatti, G. (1993). Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. *Journal of Comparativer Neurology, 338*(1), 114–140.

Madras, B. K., Xie, Z., Lin, Z., Jassen, A., Panas, H., Lynch, L., et al. (2006). Modafinil occupies dopamine and norepinephrine transporters in vivo and modulates the transporters and trace amine activity in vitro. *Journal of Pharmacology and Experimental Therapeutics, 319*(2), 561–569.

Magalona, S. C., Rasetti, R., Chen, J., Chen, Q., Gold, I., Decot, H., et al. (2013). Effect of tolcapone on brain activity during a variable attentional control task: A double-blind, placebo-controlled, counter-balanced trial in healthy volunteers. *CNS Drugs, 27*(8), 663–673.

Makris, A. P., Rush, C. R., Frederich, R. C., Taylor, A. C., & Kelly, T. H. (2007). Behavioral and subjective effects of d-amphetamine and modafinil in healthy adults. *Experimental and Clinical Psychopharmacology, 15*(2), 123–133.

McKiernan, K. A., Kaufman, J. N., Kucera-Thompson, J., & Binder, J. R. (2003). A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *Journal of Cognitive Neurosciece, 15*(3), 394–408.

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. *Journal of Neuroscience, 20*(6), RC65.

Meier, J. D., Aflalo, T. N., Kastner, S., & Graziano, M. S. A. (2008). Complex organization of human primary motor cortex: A high-resolution fMRI study. *Journal of Neurophysiology, 100*(4), 1800–1812.

Minzenberg, M. J., & Carter, C. S. (2008). Modafinil: A review of neurochemical actions and effects on cognition. *Neuropsychopharmacology, 33*(7), 1477–1502.

Müller, U., Rowe, J. B., Rittman, T., Lewis, C., Robbins, T. W., & Sahakian, B. J. (2013). Effects of modafinil on non-verbal cognition, task enjoyment and creative thinking in healthy volunteers. *Neuropharmacology, 64*, 490–495.

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews Neurosciences, 9*(11), 856–869.

Nehlig, A., Cunha, R. A., & de Mendonça, A. (2010). Is caffeine a cognitive enhancer? *Journal of Alzheimer's Disease, 20*(s1), S85–S94.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97–113.

Pauls, A. M., O'Daly, O. G., Rubia, K., Riedel, W. J., Williams, S. C. R., & Mehta, M. A. (2012). Methylphenidate effects on prefrontal functioning during attentional-capture and response inhibition. *Biological Psychiatry, 72*(2), 142–149.

Pavlova, A. A., Butorina, A. V., Nikolaeva, A. Y., Prokofyev, A. O., Ulanov, M. A., Bondarev, D. P., et al. (2019). Effortful verb retrieval from semantic memory drives beta suppression in mesial frontal regions involved in action initiation. *Human Brain Mapping, 40*(12), 3669–3681.

Price, C. J. (2010). The anatomy of language: a review of 100 fMRI studies published in 2009. *Annals of the New York Academy of Sciences, 1191*, 62–88.

Randall, D. C., Viswanath, A., Bharania, P., Elsabagh, S. M., Hartley, D. E., Shneerson, J. M., et al. (2005). Does modafinil enhance cognitive performance in young volunteers who are not sleep-deprived? *Journal of Clinical Psychopharmacology, 25*(2), 175–179.

Repantis, D., Bovy, L., Ohla, K., Kühn, S., & Dresler, M. (2021). Cognitive enhancement effects of stimulants: A randomized controlled trial testing methylphenidate, modafinil, and caffeine. *Psychopharmacology (Berl), 238*(2), 441–451.

Repantis, D., Schlattmann, P., Laisney, O., & Heuser, I. (2010). Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review. *Pharmacological Research, 62*(3), 187–206.

Retz-Junginger, P., Retz, W., Blocher, D., Weijers, H., Trott, G., Wender, P., et al. (2002). Wender Utah rating scale. The short-version for the assessment of the attention-deficit hyperactivity disorder in adults. *Der Nervenarzt, 73*(9), 830–838.

Riedel, W. J., & Blokland, A. (2015). Declarative memory. *Handbook of Experimental Pharmacology, 228*, 215–236.

Rivera-Oliver, M., & Díaz-Ríos, M. (2014). Using caffeine and other adenosine receptor antagonists and agonists as therapeutic tools against neurodegenerative diseases: A review. *Life Sciences, 101*(1-2), 1–9.

Romo, R., Hernández, A., Zainos, A., Lemus, L., & Brody, C. D. (2002). Neuronal correlates of decision-making in secondary somatosensory cortex. *Nature Neuroscience, 5*(11), 1217–1225.

Roozendaal, B., & McGaugh, J. L. (2011). Memory modulation. *Behavioral Neuroscience, 125*(6), 797–824.

Rösler, M., Retz-Junginger, P., Retz, W., & Stieglitz, R. (2008). *HASE–Homburger ADHS-Skalen für Erwachsene*. Göttingen: Hogrefe.

Sanes, J. N. (2000). Skill learning: Motor cortex rules for learning and memory. *Current Biology, 10*(13), R495–R497.

Schmaal, L., Goudriaan, A. E., Joos, L., Dom, G., Pattij, T., van den Brink, W., et al. (2014). Neural substrates of impulsive decision making modulated by modafinil in alcohol-dependent patients. *Psychological Medicine, 44*(13), 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. *Biological Psychiatry, 73*(3), 211–218.

Schmidt, A., Muller, F., Dolder, P. C., Schmid, Y., Zanchi, D., Liechti, M. E., et al. (2017). Comparative effects of methylphenidate, modafinil, and MDMA on response inhibition neural networks in healthy subjects. *The International Journal of Neuropsychopharmacology, 20*(9), 712–720.

Schmitt, M., Altstötter-Gleich, C., Hinz, A., Maes, J., & Brähler, E. (2006). Normwerte für das vereinfachte Beck-Depressions-Inventar (BDI-V) in der Allgemeinbevölkerung. *Diagnostica, 52*(2), 51–59.

Scimeca, J., & Badre, D. (2012). Striatal contributions to declarative memory retrieval. *Neuron, 75*(3), 380–392.

Sharma, A., & Couture, J. (2014). A review of the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). *The Annals of Pharmacotherapy, 48*(2), 209–225.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59 Suppl 20*, 22–33;quiz 34–57.

Shergill, S. S., Bullmore, E. T., Brammer, M. J., Williams, S. C. R., Murray, R. M., & McGuire, P. K. (2001). A functional study of auditory verbal imagery. *Psychological Medicine, 31*(2), 241–253.

Shuman, T., Wood, S. C., & Anagnostaras, S. G. (2009). Modafinil and memory: Effects of modafinil on Morris water maze learning and Pavlovian fear conditioning. *Behavioral Neuroscience, 123*(2), 257–266.

Simonyan, K., Herscovitch, P., & Horwitz, B. (2013). Speech-induced striatal dopamine release is left lateralized and coupled to functional striatal circuits in healthy humans: A combined PET, fMRI and DTI study. *Neuroimage, 70*, 21–32.

Smith, A. (2002). Effects of caffeine on human behavior. *Food and Chemical Toxicology, 40*(9), 1243–1255.

Squire, L. R., Genzel, L., Wixted, J. T., & Morris, R. G. (2015). Memory consolidation. *Cold Spring Harbor Perspectives in Biology, 7*(8), a021766. https://doi.org/10.1101/cshperspect.a021766.

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience, 27*(1), 279–306.

Swanson, J. M., & Volkow, N. D. (2003). Serum and brain concentrations of methylphenidate: Implications for use and abuse. *Neuroscience & Biobehavioral Reviews, 27*(7), 615–621.

Takahashi, R. N., Pamplona, F. A., & Prediger, R. D. (2008). Adenosine receptor antagonists for cognitive dysfunction: A review of animal studies. *Frontiers Bioscience, 13*, 2614–2632.

Tomasi, D., Volkow, N. D., Wang, G. J., Wang, R., Telang, F., Caparelli, E. C., et al. (2011). Methylphenidate enhances brain activation and deactivation responses to visual attention and working memory tasks in healthy controls. *Neuroimage, 54*(4), 3101–3110.

Turken, A. U., & Dronkers, N. F. (2011). The neural architecture of the language comprehension network: Converging evidence from lesion and connectivity analyses. *Frontiers in Systems Neuroscience, 5*, 1.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273–289.

Ullrich, S., de Vries, Y. C., Kühn, S., Repantis, D., Dresler, M., & Ohla, K. (2015). Feeling smart: Effects of caffeine and glucose on cognition, mood and self-judgment. *Physiology & Behavior, 151*, 629–637.

Volkow, N. D., Fowler, J. S., Wang, G.-J., Telang, F., Logan, J., Wong, C., et al. (2008). Methylphenidate decreased the amount of glucose needed by the brain to perform a cognitive task. *Public Library of Science One, 3*(4), e2017.

Volkow, N. D., Wang, G., Fowler, J. S., Logan, J., Gerasimov, M., Maynard, L., et al. (2001). Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *Journal of Neuroscience, 21*(2), RC121.

Volkow, N. D., Wang, G. J., Logan, J., Alexoff, D., Fowler, J. S., Thanos, P. K., et al. (2015). Caffeine increases striatal dopamine D2/D3 receptor availability in the human brain. *Translational Psychiatry, 5*(4), Article e549.

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., et al. (1998). Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity. *Science, 281*(5380), 1188–1191.

Wagner, I. C., van Buuren, M., Bovy, L., Morris, R. G., & Fernández, G. (2017). Methylphenidate during early consolidation affects long-term associative memory retrieval depending on baseline catecholamines. *Psychopharmacology (Berl), 234*(4), 657–669.

Wasaka, T., Nakata, H., Akatsuka, K., Kida, T., Inui, K., & Kakigi, R. (2005). Differential modulation in human primary and secondary somatosensory cortices during the preparatory period of self-initiated finger movement. *The European Journal of Neuroscience, 22*(5), 1239–1247.

Wechsler, D. (1981). *WAIS-R manual: Wechsler adult intelligence scale-revised*. Psychological Corporation.

Weiß, R., Albinus, B., & Arzt, D. (2006). *Grundintelligenztest Skala 2-Revision (CFT 20-R)*. Hogrefe.

Wood, S., Sage, J. R., Shuman, T., Anagnostaras, S. G., & Sibley, D. R. (2014). Psychostimulants and cognition: A continuum of behavioral and cognitive activation. *Pharmacological Reviews, 66*(1), 193–221.

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 in Biomedicine, 27*(4), 444–452.

Ziegler, W. (1997). The role of the left mesial frontal cortex in fluent speech: Evidence from a case of left supplementary motor area hemorrhage. *Neuropsychologia, 35*(9), 1197–1208.