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DISSERTATION

Functional Imaging in Neuroenhancement

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List of Abbreviations

A_x = Adenosine receptor

ACC = anterior cingulate cortex

ADHD = Attention deficit hyperactivity disorder

AMP = Amphetamine

ASL = Arterial spin labeling

BDNF = Brain-derived neurotrophic factor

BOLD effect = Blood-oxygen-level-dependent effect

CAF = Caffeine

CBF = Cerebral blood flow

CFT = Cultural-Fair-Test

CNS = Central nervous system

DA = Dopamine

DAN = Dorsal attention network

D_x = Dopamine receptor type

DLPFC = dorsolateral prefrontal cortex

DSST = Digit-symbol-substitution-task

ECG = cardiogram

EEG = electro encephalography

EHI = Edinburgh Handedness Inventory

EPI = Echo planar imaging

FC = Functional connectivity

fMRI = functional magnet resonance imaging

FoV = Field of View

FPC = Frontal parietal control

FWE = Family wise error

GLM = General linear model

HR = Heart rate

IPL = Inferior parietal lobe

ITL = Inferior temporal lobe

LGT = Lern- und Gedächtnistest

MCC = medial cingulate cortex

MOD = Modafinil

MPH = Methylphenidate

MTL = Medial temporal lobe

NAc = Nucleus accumbens

NA = Noradrenaline/norepinephrine

NET = Norepinephrine transporter

NE = Neuroenhancement

NIRS = Near infrared spectroscopy

PCC = Posterior cingulate cortex

PD = Parkinson's disease

PFC = Prefrontal cortex

PLA = Placebo

RL = Reversal learning

ROI = Region-of-Interest

RR = blood pressure

RS = Resting state

RT = Reaction time

SMA = Supplementary motor area

SN = Substantia nigra

SWM = Spatial working memory

TE = Time of echo

TID = Task-induced deactivations

TR = Time of Repetition

VTA = Ventral tegmental area

VLPFC = ventrolateral prefrontal cortex

VMPFC = ventromedial prefrontal cortex

MWT = Mehrfachwahl-Wortschatz-Intelligenztest

Zusammenfassung

Zunehmende Arbeitsbelastung, erhöhter Zeitdruck und größere Verantwortung haben dazu geführt, dass für Studenten und Arbeitnehmer das Phänomen Neuroenhancement (NE) eine zunehmende Relevanz erlangt hat. Darunter wird die Steigerung der kognitiven Leistung durch pharmazeutischen Eingriff auf zentralnervöse Prozesse verstanden. Substanzen wie z.B. Methylphenidat (Ritalin®), Modafinil (Vigil®) und Koffein gelten als aussichtsreiche Kandidaten zur Leistungssteigerung, die möglicherweise Einfluss auf kognitive Prozesse, wie z.B. Exekutive Funktionen, Inhibitionskontrolle und Gedächtnis ausüben können (Wood et al., 2014). Keine bisher publizierte Studie hat den Fokus auf neuronale Korrelate der deklarativen Gedächtnissteigerung gelegt. Aus dem Grund sind zusätzlich alle bisher veröffentlichten bildgebenden Studien zu Methylphenidat, Modafinil und Koffein zu einer strukturierten Übersicht zusammengefasst worden.

Mittels funktionaler Magnetresonanztomographie (fMRT) wurden 48 gesunde Probanden, doppelt verblindet und randomisiert auf Steigerung der deklarativen Gedächtnisleistung getestet. Obwohl die Wirksamkeit der drei Substanzen ausführlich für klinische Patientenpopulationen untersucht wurde, gibt es kaum Wissen über die möglichen behavioralen und neuronalen Auswirkungen auf gesunde, erwachsene Menschen.

Entgegen der Erwartung, dass die getesteten Substanzen klassische Gedächtnis assoziierte Regionen aktivieren, wurden unterschiedliche substanzspezifische Effekte gefunden. Wahrend des Abrufs von Gedächtnisinhalten deaktivierte Methylphenidat fronto-parietale und temporale Regionen. Dagegen führte die Applikation von Koffein zu einer verringerten BOLD Antwort im Gyrus Präcentralis während der Lernphase. Modafinil führte zu keiner Veränderung im Vergleich zu Placebo. Auf Verhaltensebene förderte Methylphenidat den späten Abruf von Gedächtnisinhalten, wohingegen die beiden anderen Substanzen keine Effekte hinsichtlich der Lernleistung vorwiesen. Vor dem Hintergrund bisheriger bildgebender Studien zeigt die vorliegende Arbeit, dass Neuroenhancement neben der Aktivierung leistungsrelevanter Gehirnregionen auch durch Reduzierung von störenden Einwirkungen funktionieren kann und damit womöglich die Effektivität der Informationsverarbeitung erhöht.

Schlagwörter: Neuroenhancement, Methylphenidat, Modafinil, Koffein, Deklaratives Gedächtnis, fMRI

Abstract

Increasingly demanding tasks, competition for competence and time pressure have lead to attempts of neuroenhancement (NE) among students and employees. NE is designed to increase cognitive abilities by modulating brain processes through the use of pharmaceutics.

Substances such as methylphenidate (i.e. Ritalin®), modafinil (i.e. Vigil®) and caffeine are common candidates for enhancing cognitive abilities such as executive functions, inhibition control and memory (Wood et al., 2014). Until today, there has not been a study investigating memory enhancement in functional magnetic resonance imaging (fMRI).

Using fMRI, 48 healthy participants were tested for drug effects in a single-dose, double-blind and randomized study using a declarative memory task. During memory recall, methylphenidate dependent deactivations were found in the fronto-parietal and temporal regions whereas no BOLD alterations were seen during encoding. On the behavioral level, methylphenidate enhanced subject's judgement confidence and performance during late recall. During encoding, caffeine led to deactivations in the precentral gyrus whereas modafinil did not show any BOLD signal alterations at all.

To get an overview over the existing neuroimaging literature, all published studies on the effects of the aforementioned drug agents were reviewed in addition. In line with this study, previous publications emphasized that methylphenidate seems to alter task relevant brain areas. Our main finding of task-related deactivations may point to the reduction of task-functioning distractions. Thereby, we conclude a drug-dependent increase of efficiency in data processing.

Key words: Neuroenhancement, methylphenidate, modafinil, caffeine, declarative memory, fMRI, imaging

1. Introduction

We've all been there, those moments in life when there is too little time for an important task set... The manager who has to complete a project within three days and is despairing because work demands are plain unrealistic but expected; the sleep-deprived student who pulls an all-nighter to finish her assignment in an environment of competition and pressure; the multi-tasking single mum who juggles several jobs on top of childcare and ends up with no time for herself... Wouldn't it be nice to have a little bit of support in these difficult situations with a stimulant to at least stay 'focused'?

Increasing demands, staff shortages and time pressure force employees and students to find alternative solutions to achieve their goals in career. Among other strategies, a certain portion of the labour force and students find a remedy through pharmaceutical backup (Förstl, 2009). A recent survey even revealed consumption of stimulants among scientists (Maher, 2008). Also called smart drugs, nootropics or just neuroenhancers, a wide range of pharmaceutics are used because they are supposed to improve cognitive skills and abilities - even though their actual field of indication is much different.

The desire to overcome cognitive limitations in humans has had a long tradition in different cultures over the centuries (Rose, 2002). Also today, people reckon that the current level of performance and cognition in the human race is not the end of the line. Two questions arise: What are our limits of attention, performance and learning? And is there a way of overcoming them?

The conventional way of improving performance is cognitive training. Repetitive execution of the same task leads to deeper processing of acquired behaviour and skills (Hebb, 1949); hence faster and better results (Nelson, 1977). Returning to the example of the manager working under time pressure, it is obvious that there is not enough time to perform the task to his satisfaction. An external approach for neural modulation may rely on the application of pharmaceutical stimuli that are also able to modulate and strengthen cortical organisation. Known from competitive sports and military service, pharmaceutical substances are already used to modulate performance, mood or even personality (Rose, 2002). Concerning cognition, many different candidate drugs are rumoured to be effective in reducing reaction time, increasing accuracy or just perseverance in long–term tasks.

In fact, the neurological processes behind neuroenhancement (NE) are not fully comprehended so far, even though epidemiological studies show that augmented

consumption of neuroenhancers is a widespread phenomenon. Nevertheless, the fledgling discipline of NE is also accompanied by a sharp debate about ethical circumstances that may bias research and perception of NE. Based on the increasing relevance of this contentious topic, the aim of this medical dissertation is to investigate the neuronal effects of methylphenidate, modafinil and caffeine during a memory task. A sample of 48 healthy adults participated in this randomized double-blind crossover fMRI experiment.

2. Background

Different authors have a different understanding of the term pharmaceutical NE. For Hall (2004), the concept of NE encompasses a cognitive domain-specific improvement in attention, mood and memory, whereas other authors expand on this definition by taking vaccinations and prophylaxis into account (i.e. Lev et al., 2010). The strengthening of cognition is also subject of machine-supported treatments such as deep brain stimulation and light therapy (Suthana & Fried, 2014; Riemersma-van der Lek et al., 2008). Furthermore, food supplements such as vitamins and phytopharmaceuticals as well as endogenous substances such as brain-derived neurotrophic factor (BDNF) may also act as sources for neuronal enhancement (Förstl, 2009; Dresler et al., 2013). However, this dissertation limits itself to examining the effects of pharmaceutical NE and excludes all other forms of stimulation.

Instead of being based on a too narrow or too blurry notion, this study defines pharmaceutical NE as the "improvement in the cognitive, emotional and motivational functions of healthy individuals through […] the use of drugs" (Repantis, Schlattmann, Laisney & Heuser, 2010, pp. 187). Furthermore, NE differs from medical healthcare in its target population: Instead of patients, exclusively healthy volunteers are subject of NE. Although adopting methods of biomedical research, NE does not aspire to healing or intend to treat diseases.

Pharmaceutical neuroenhancers are derived from drugs or substances that are typically indicated for patients with specific diseases. Typically, there is a large body of evidence on how these substances successfully affect patients during general treatment. However, many of these substances are misused by healthy people to enhance their cognitive functions. Indeed, if it helps improving the sick, why shouldn't it work on the healthy? Although there is no authoritative source of information about pharmacological effects in healthy populations, presumably an increasing number of healthy people use drugs in daily life situations (Repantis et al., 2010). Pharmaceutical NE is the umbrella term for all sorts of agents that are suspected to improve a certain feature. For example, consumers take antidepressants, vasopressin and amphetamine derivatives to enhance attention; adrenaline and glucose for learning improvement; neurosteroids and growth factors for a better memory maintenance (Rose, 2002). Furthermore there are reports of NE through sex hormones (Pintzka & Håberg, 2015), β-blockers and other drugs (Förstl, 2009).

In addition to medical questions, there is an active debate regarding ethical considerations of neuroenhancement. Basically, the critical debate can be broken down into three major areas: safety aspects, market liberalisation and competition fairness (Farah et al., 2004). The topic touches academic fields of medical biosciences, law and philosophy and, accordingly, leads us to different evaluations. In critical, philosophical contributions, NE research is criticized for its consequences for the individual as well as negative implications for society (Schöne-Seifert & Talbot, 2009). An even more pessimistic view compares current approaches to enhancement of human performance to eugenic methods used by the Nazi regime (Habermas, 2001). Perhaps those fears arise from wrong presumptions concerning potential effects of neuroenhancers. Many arguments are based on the perception that we are close to finding a drug that clearly enhances cognition without producing any side-effects (i.e. Synofzik, 2010). In fact, this view on effectivity is largely unsupported by current empiric data on neuroenhancement (Repantis et al., 2010). This lack of evidence caused other authors to dismiss fears and dystopian thoughts within the ethical debate. For instance, Quednow (2010) described those ideas as pure "futurology" and critically noted that the current debate deals with "the ethical consequences of new technologies before they are fully developed" (pp. 155-156). Whether research is justified in such a controversial ethical field is another point of contention within the enhancement debate. Whereas one side demands stricter regulation by law or even a strict research prohibition (Schöne-Seifert, 2010), others favour liberation to promote new opportunities (Gesang, 2006). This inconsistency may be due to the ambiguity that exists about drug effects, the spread of consumption and professional perspective of critics in that discussion.

Due to the high prevalence of users among young educated people in their early twenties (Sussman, Pentz, Spruijt-Metz, & Miller et al., 2006), much of the current literature on NE pays particular attention to college students and their need of coping with stress and cognitive requirements (for review, see Finger et al., 2013). Interestingly, the distribution and availability of pharmaceutical neuroenhancers vary significantly among students. The prevalence margin differs between countries (Micoulaud-Franchi, 2014; Schelle et al., 2015, Deligne et al., 2014) and even between universities in the US (McCabe, Knight, Teter, & Wechsler, 2005). Cultural differences, differences in drug market regulation and student design may explain some of the varying results. At this point, it should be noted that many so-called neuroenhancers are also recreationally consumed for reasons that are not related to performance

improvement. For example, methylphenidate (MPH), a common smart drug with similarities to amphetamine (Sulzer et al., 2005), has potential for mood lifting, getting 'high' or act as a party drug (Sussman et al., 2006). Although the fact that not every drug is meant for performance enhancement, do enhancement consumers gain benefits through their drug consumption? How do we deal with habitual non-users? Do they have a disadvantage when it comes to exams and competition? What about fairness aspects?

The moral questions cannot be sufficiently answered if we do not take a further look at the actual effectivity of smart drugs. In a meta-analysis on the effect of MPH and modafinil (MOD) on healthy adults, Repantis et al. (2010) stated that there was no hope for these candidates to act as reliable neuroenhancers. MPH could partly enhance short-term memory and attention, whereas MOD temporarily improved performance particularly in sleep-deprived subjects in the domain of memory and executive functions. Interestingly, the authors found subjects to overestimate their performance when medication was applied. In line with this impression based on a survey among clinical surgeons, Franke et al. (2014) warns of risks through overestimation after NE consumption. Similarly, other authors cautioned against the subjective impression of improved performance without any effect in "the real world" (Advocat & Scheitheuer, 2013). Other problems in this regard may concern the abuse and also side effects such as risky behaviour (Advokat & Scheitheuer, 2013).

Taken together, NE is currently one of the most controversial research fields in modern biomedical science. Despite ethical issues, an increasing number of people take drugs to increase their abilities. Especially students seem to promote their learning skills through neuroenhancers. Previous research approached neuroenhancement in the assessment of different cognitive functions whereas the link to the real world remained questionable. The memory domain seems to be the most common ability that NE consumers seek to enhance. Therefore, possible improvement of memory performance needs to be further assessed.

2.1 Declarative Memory

During the experiment, subjects were asked to encode and retrieve information from their memory whilst being under influence of a placebo or a stimulant. The declarative memory is part of the human memory system. It can be subdivided into episodic and semantic memory. Both types have their neuronal representation in a network including hippocampus, prefrontal and cortical regions (Borst & Anderson, 2013; Squire, Stark & Clark 2004). While semantic memory stores facts, i.e. meaning of words and world-knowledge, episodic memory stores memories of experienced events and situations, i.e. autobiographical knowledge. Both processes are necessary to successfully encode and recall knowledge and facts (Tulving, 2002). Usually, experiments on healthy subjects use word list paradigms to assess declarative verbal memory (Riedel & Blokland, 2015). Through the learning of word lists, all three phases of the memorization process can be detected: encoding, consolidation and recall. During the encoding process, new information is obtained and stored in short-term memory. Memory deterioration is avoided through the consolidation of perceived information into the long-term memory storage, i.e. through rehearsal strategies. The retrieval phase is characterized either through the recognition of consolidated knowledge or its spontaneous recall.

As a neuroanatomical substrate for these processes, the interplay of the prefrontal cortex (PFC) and the medial temporal lobe (MTL) was identified (Simons & Spiers, 2003). A crucial role for the encoding phase can be allocated to the hippocampus, which interacts between PFC and parahippocampal cortex. Graphically speaking, the hippocampus gates new information towards neocortical regions where they later become restructured, i.e. during sleep and rest periods (Stickgold, 2005). Prefrontal areas seemingly support directed memory recollection, strategic learning as well as monitoring (Henson, Shallice, & Dolan, 1999). During semantic memory processing, a lateralization of cortical activation was discovered, whereas left hemispherical processes are more associated with encoding and the right hemisphere with retrieval. Depending on the stimuli material, a tendency for lateralization during both encoding and retrieval was also found for verbal and non-verbal stimuli, which showed stronger activations in the left or right PFC, respectively (Habib, Nyberg, & Tulving, 2003). Besides animal literature, clinical trials and single case studies, recent findings of neuro-imaging studies brought new insights into memory processes. Whereas encoding is mainly attended by hippocampal activation (Kim, 2011), imaging studies on retrieval are less clear (Cabeza & Nyberg, 2000; Takashima et al., 2006). In healthy, non-

medicated subjects, activations related to retrieval were seen in prefrontal areas (Dupont et al., 2000; Alessio et al., 2013), anterior cingulate cortex (ACC, Borst & Anderson, 2013) and also the hippocampus (Hayes, Ryan, Schnyer, & Nadel, 2004). A model-based fMRI review on different memory entities could show a wide range of overlapping activations in the fronto-parietal network between declarative and working memory. Unlike working memory, declarative memory retrieval correlates to large activations in the inferior frontal gyrus (Borst & Anderson, 2013).

From clinical trials on schizophrenia and Parkinson's disease (PD), it is well known that these patients suffer from a reduced working memory (Goldman-Rakic, 1995). Both diseases are formed by distinct pathologies; however, both have a lack of optimal dopamine (DA) sensitivity in common (Dauer & Przedborski, 2003; Howes & Kapur, 2009). Neurons of the PFC containing high density of dopaminergic D_1 receptors play a crucial role in working memory functioning. Located in the substantia nigra (SN) and ventral tegmental area (VTA), the dopaminergic cells of the central nervous system (CNS) project primarily to limbic, striatal and cortical areas (Wise, 2004). An optimal DA metabolism in frontal brain areas seems to be indispensable for successful cognitive operations (Williams & Goldman-Rakic, 1995). Additionally, a prominent role of DA could also be established for other regions within the memory framework, such as the VTA, the hippocampus and the striatum (Lisman & Grace, 2005; Scimeca & Badre, 2012). The increased release of DA in the CNS positively affects hippocampal memory consolidation and activates prefrontal regions (Wise, 2004). A possible molecular mechanism of memory forming may be a DA-dependent protein synthesis during the consolidation process (Lisman, Grace & Duzel, 2011).

A deeper understanding of the pathology of memory retrieval has fuelled expectations for potential therapies and prevention steps against cognitive decline. In recent years, these insights reached the field of NE. In other words, healthy people with normal memory function sought memory improvement through pharmaceutical self-treatment. Riedel & Blokland (2015) reviewed the literature for memory enhancement during the last ten years. Among other metabolites, DA is the most frequently explored transmitter with regard to memory enhancement. Drugs that affect the central DA system are d-amphetamine, methylphenidate, tolcapone and Levo-Dopa. Indirectly, modafinil and caffeine also influence DA metabolism.

2.2 Methylphenidate

Rapidly growing prescription rates of methylphenidate (MPH, methyl 2-phenyl-2-(piperidin-2-yl)acetate) has become a global phenomenon (Scheffler et al., 2007). Besides atomoxetine and dextroamphetamine, MPH is the first-line pharmaceutical used for treatment of attention-deficit/hyperactivity disorder (ADHD, del Campo et al., 2013), which is said to be the mental disorder with the highest prevalence amongst children worldwide - from 5.9 to 7.1% (Willcutt, 2012). ADHD is characterized by a deficit in the domains of attention, impulsivity and hyperactivity. As a pathomechanism of ADHD, a dysregulated fronto-striatal catecholamine pathway is discussed. Tonic DA release is lowered in these regions, whereas sudden high bursts of DA occur from time to time, thereby leading to the aforementioned symptoms. A normalization of DA level i.e. by MPH, can reduce the phasic DA efflux and may lead to a visible decrease in ADHD symptoms and normalization of cognitive deficits (Sharma & Couture, 2014).

The active metabolites of MPH are the *dl-threo*-racemates, whereas the *d*-enantiomer has the highest pharmacological potency (Kimko, Cross, & Abernethy, 1999). While MPH's mechanism of action is not fully understood so far, it seems that *d-threo*-MPH increases DA and noradrenaline/norepinephrine (NA) in prefrontal areas as well as in the hippocampus and striatum by inhibiting the reuptake of these catecholamines (Markowitz, 2006; Moeller et al., 2014). MPH dose determines drug effect magnitude as well as effect localisation (Wilens, 2008). The antagonistic bindings at the dopamine transporter (DAT) as well as at the norepinephrine transporter (NET) lead to an increase of these neurotransmitters within the synaptic cleft. Furthermore, MPH presumably has low binding ability to 5-HT_{1A} and other receptors (Markowitz & Patrick, 2008; Zhang et al., 2012). Besides these short-term effects caused by single dose application, there are also reports about long-term structural and functional consequences of a permanent MPH therapy (Gray et al., 2007).

MPH reaches a peak effect in plasma concentration 1 to 3 hours after oral administration (Srinivas et al., 1993; Kimko et al., 1999). Passing the blood-brain barrier easily due to lipophilic attributes, notable MPH levels in the striatum can already be detected 5-15 minutes after i.v. injection (Volkow et al., 1995). After 8 to 48 hours, 50 to 90% MPH is eliminated from the body and nearly completely excreted in the urine (Kimko et al., 1999).

The recommended therapeutic dose for adults lies between 10 and 60 mg in three daily doses. Adverse effects are dose-dependent and are expected from 2 mg/kg and above. In

children and adults suffering from ADHD, MPH has shown to be an effective therapy (Sharma & Couture, 2014). Nevertheless, its adverse side effect and drug interaction profile should also be taken into account before prescribing. Beside somatic side effects such as tachycardia, increased blood pressure, decreased appetite, nausea, MPH may also lead to undesired mental effects such as emotional instability, overfocusing and reduction in cognitive flexibility (Kimko et al., 1999; Sharma & Couture, 2014).

Animal studies on the effect of low-dose MPH indicated a link between DA discharge within the PFC and improvement of working memory (Arnsten & Dudley, 2005; Berridge et al., 2006), sustained attention but not control inhibition (Andrzejewski et al., 2014). In contrast, high doses of MPH in rats, rather increase hippocampal NA release (Kuczenski & Segal, 2002). In line with this, another group could demonstrate an enhancement effect of MPH for fear and long-term memory (Carmack, Block, Howell, & Anagnostaras, 2014). In conclusion, these results indicate that MPH enhances performance of different cognitive domains by amplifying DA and NA availability in different brain regions.

Similarly, in humans, MPH was found to improve several cognitive abilities (Elliott et al., 1997; Mehta et al., 2000). Two different groups summarized cognitive enhancing effects caused by the application of MPH in healthy humans (Linssen, Sambeth, Vuurman, & Riedel, 2014; Repantis et al., 2010). Surprisingly, the results do not match. Whereas Repantis et al. (2010) mentioned MPH-related benefits for memory function; no improvements for other domains were found. In contrast, Linssen et al. (2014) noted MPH to be effective in working memory, speed of processing, verbal learning and memory, attention and vigilance, reasoning and problem solving, but not in visual learning and memory. This distinction may lie in a different method of study selection and weighting of sample size. In addition, Linssen et al. (2014) specified psychological domains broadly and took different dose ranges into account, whereas Repantis et al. (2010) focussed on single-dose treatment. Besides differences in dosage, there are reports about varying drug effects regarding subject baseline performance. For instance, Mehta et al. (2000) demonstrated that subjects with low working memory capacity benefited considerably more from taking MPH than their counterparts with higher baseline performance. Generally, it seems that amphetamines enhance performance relying on prefrontal cortex function in dependence on baseline scores (Mattay et al., 2003). As an explanation, Wood et al. (2014) proposed that lower baseline ability is associated with sub-optimal DA concentration within the prefrontal areas. Thus, a

restoration of an optimal DA transmitter equilibrium, e.g. through stimulant administration, may lead to enhanced executive functioning. This has indeed been shown before at least for the cognitive function of sustained attention (Del Campo et al., 2013). Independent of diagnosis, ADHD patients and controls with low baseline performance improved their performance and normalized their caudate activity after MPH application. On the other hand, no further improvements could be seen in subjects that already scored high in the placebo condition.

With regard to declarative memory, there is evidence that MPH enhances performance of ADHD patients (Peeke et al., 1984; Verster et al., 2010). Whether MPH affects cognitive domains in healthy adults is controversial: some studies could not identify significant benefits of MPH on the recall of word lists (Kuypers & Ramaekers, 2005; Hermens, Cooper, Clark, Lilly, & Clarke, 2007), whereas other researchers have reported an MPH-dependent enhancing effect for 20 mg and 40mg on word list learning (Linssen, Vuurman, Sambeth, & Riedel, 2012).

In a meta-analysis on brain activation effects of MPH among ADHD children, Czerniak and colleagues (2014) found a tendency for MPH to activate the frontal lobe, basal ganglia and the cerebellum – typical areas in which deficits have been related to ADHD. Dependent on the cognitive task, MPH also acts in a varied fashion in different brain regions in healthy adults (Table 1).

MPH produces different effects when given during resting period compared to cognitive task requirements. From imaging studies using positron emission tomography (PET), it is known that MPH activates the striatum during resting periods (Del Campo et al., 2013; Volkow et al., 2001). In addition, MPH leads to deactivations in functional connectivity (FC) between striatum and the midbrain (Honey et al., 2003). However, this result should be taken into account with caution due to the relatively old age of the study population (Ø 72 years). Task-specific effects of MPH differ with regard to cognitive demands, difficulty, subject baseline performance as well as task design. To assess MPH effects on working memory, different tasks were performed. Spatial search paradigms revealed activations in the ventral striatum (Clatworthy et al., 2009), posterior cingulate cortex (PCC), precuneus and ventromedial PFC (VMPFC) during encoding (Marquand, Simoni, Moura, & Mehta, 2011). In contrast, deactivations were also found in the left dorsolateral PFC (DLPFC), left PPC, left supplementary motor area (SMA) (Mehta et al., 2000), insula and PCC (Tomasi et al., 2011), PCC, precuneus, VMPFC (Marquand et al., 2011). Using a reversal learning task, authors could identify blood-oxygen-level-

dependent (BOLD) signal deactivations in the putamen, cuneus, precentral gyrus (Dodds et al., 2008), caudate nucleus (Clatworthy et al., 2009) and right inferior frontal gyrus and insula during successful and failed inhibitions (Pauls et al., 2012). Furthermore, the assessment of task switching revealed deactivations in ventrolateral PFC (VLPFC) and ACC (Dodds et al., 2008).

During attention assessment, application of MPH led to increased BOLD response in precentral gyrus, inferior parietal gyrus, precuneus (Müller et al., 2005), ACC, temporal poles, SMA, cerebellum (Udo De Haes, Maguire, Jager, Paans, & Den Boer, 2007), bilateral caudate nucleus, motor cortex, right inferior PFC, cerebellum (Farr et al., 2014), while decreased BOLD signal was found in superior temporal gyri, right medial frontal gyrus and right inferior parietal cortex (Udo De Haes et al., 2007). No drug effect was found during a simple motor response task (Rao et al., 2000).

Findings on error processing suggested that MPH affects BOLD signal increases in the ACC, medial frontal gyrus (Pauls et al., 2012) and right putamen during unsuccessful inhibition (Costa et al., 2013). In contrast, during wrong responses in the Stroop test, activity in the ACC was attenuated by taking MPH (Moeller et al., 2014). During uncertainty processing, MPH dependent activations were seen in the gyrus parahippocampalis, ACC, cerebellum and precentral gyrus, while placebo leads to BOLD signal increases in Parietal cortex and PCC (Schlösser et al., 2009).

In summary, interaction between MPH and task requirements led to a diverse pattern of activation and deactivation in different brain regions. Noteworthy, most functional findings did not correlate to significant behavioural benefits of MPH intake.

Until now, no imaging study has focused on MPH effects on declarative memory. Only Chowdhury et al. (2012) performed a pattern recognition task on healthy older subjects and compared brain activity between remembered and forgotten words. After applying L-DOPA, a precursor of DA agonist, they discovered increased activation in the hippocampus that may constitute a brain area that can also be potentially enhanced by MPH.

Table 1. Imaging studies comparing MPH and PLA in healthy adults

Study	N	Method	Dose	Cognitive domain	Test paradigm	Behavioural effects	Imaging effects
Working 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 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 in 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* 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*: increase 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
Marquand, Simoni, Moura, & Mehta, 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

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, Maguire, Jager, Paans, & Den Boer, 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
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
Error Processing							
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 trials* Activations 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
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
Resting							
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	Resting	-	-	ROI Striatum: Increase in DA ROI Cerebellum: No effect
Zhu et al., 2013	18	RS fMRI	20 mg	Resting state	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)

MeSH terms: methylphenidate AND imaging OR MRI OR fMRI OR PET OR SPECT, scanning pubmed database and scholar.google.com, inclusion of healthy adults, exclusion of subjects younger than 18 years and history or presence of mental and physical diseases, study publication dates between 1990 and December 2015, only publications in English language, 0.5 mg/kg MPH ≈ 40 mg for an adult man of 80 kg, MPH>PLA = main drug effect, MPH X Task = interaction between drug and task, RS = Resting state, l = left, r = right.

2.3 Modafinil

Modafinil (MOD, 2-[(Diphenylmethyl)sulphinyl]acetamide) is another pharmaceutical stimulant that is discussed as a neuroenhancer. First administered in France in the early 1990s, MOD was approved for narcolepsy due to its awaking properties (Dauvilliers, Billiard, & Montplaisir, 2003). Narcolepsy is characterized by a loss of cataplexy and excessive daytime sleepiness due to an imbalance in central nervous DA and acetylcholine systems. The pathology of these transmitter alterations is presumably caused by a deficiency of hypocretine (orexin) in the hypothalamus (Liblau, Vassalli, Seifinejad, & Tafti, 2015). In elevating extracellular catecholamines and, indirectly, activating the hypocretinergic system, MOD effectively reduces symptoms in sleeping disorders (Minzenberg & Carter, 2008). Nowadays it is widely prescribed for several more diseases that are associated with daytime sleepiness conditions (Ballon & Feifel, 2006), affective disorders (Corp, Gitlin, & Altshuler, 2014) and schizophrenia (Scoriels, Jones, & Sahakian, 2013). Further MOD consumption may be explained by the use for potential cognitive enhancing effects (Battleday & Brem, 2015).

The biochemical profile and structure of MOD clearly differ from amphetamine-like stimulants such as MPH. MOD affects a wide range of transmitter systems and involves ramifications in different brain areas (for review: Scoriels et al., 2013). Primarily, MOD moderately elevates catecholamines through the inhibition of DAT and NET. Secondary effects are found in the promotion of glutamate, 5-HT, histamine, and hypocretine pathways, whereas GABAergic transmission is diminished. In general, MOD predominantly affects cortical areas of the frontal lobe and shows minor activity in subcortical sites (Minzenberg & Carter, 2008).

MOD consists of two equipotent Enantiomers (*d*-*l*-MOD) and reaches its highest plasma concentration after 2 to 4 hours. With a halftime of 12 to 15 hours, metabolization is mostly achieved in the liver and excretion in the urine (Robertson & Hellriegel, 2003). MOD appears to interact with several pharmaceuticals due to CYP2C19 inhibition and CYP3A5 induction (Minzenberg & Carter, 2008). No interaction effects with methylphenidate were reported (Wong et al., 1998).

Unlike MPH, MOD produces lower rates of addiction as well as reduced somatic side effects (Minzenberg & Carter, 2008). Most prevalent side effects are headache, nausea, nervousness, anxiety and insomnia (Robertson & Hellriegel, 2003). During a continuous therapy of 40 weeks, subjects on MOD reported significant clinical improvements,

whereas neither tolerance effects nor lasting harm occurred (Mitler, Harsh, Hirshkowitz, & Guilleminault, 2000).

Reports on animal studies are inconsistent (Wood et al., 2014). This may be due to different designs and dose ranges used. It is likely that MOD enhances memory function in a very selective and dose-dependent fashion. Mice could improve spatial memory at high doses, however, they showed memory disruptions at the same dose in a fear-conditioning paradigm. Furthermore, time of application influenced the test outcome. MOD only improved recall when given before the training session. This may implicate a sole modulation of encoding processes (Shuman, Wood, & Anagnostaras, 2009).

In humans, research on sleep-deprived adults found MOD to effectively improve cognitive functions (Repantis et al., 2010). Furthermore, there is evidence that MOD acts as an enhancer in non-sleep-deprived adults. While MOD inconsistently showed cognitive improvements during simple working memory tasks (i.e. Turner et al., 2003), there was stronger support for cognitive improvement among subjects performing more demanding exercises (Battleday & Brem, 2015). The domains of attention, learning and executive functions got improved through MOD, especially during complex tasks such as probability learning at varying levels of difficulty.

For memory function in particular, there also seems to be a positive drug effect. Although another paradigm than word list learning was used, two research groups showed that MOD enhances declarative memory in pattern recognition more than placebo (Müller et al., 2013; Randall, Viswanath et al., 2005). Besides advanced results in working memory tasks, Müller and colleagues (2013) found that delayed recognition of patterns improved after taking MOD. However, the authors point out that subjects benefit from drug intake just in the highest difficulty in these tasks. Furthermore, they could not find any MOD effects in paired associates learning. In contrast, a significant improvement in short-term memory and pattern recognition but no effect in delayed memory was found in another study comparing the effects of 100 mg and 200 mg of MOD and placebo (Randall, Viswanath, et al., 2005). However, similar to the aforementioned observations in MPH, the authors pointed out the relationship between baseline performance and drug effect (Randall, Shneerson, & File, 2005). In a retrospective manner, they re-examined results of prior published studies with regard to subjects' intelligence. In doing so, they found an interaction effect of MOD and intelligence regarding speed and vigilance, indicating an emphasized sensitivity of MOD

enhancement effects, especially in subjects with lower IQ (mean = 106 ± .6) compared to the higher IQ group (mean = 115 ± .5).

No imaging studies on MOD's effect on verbal memory have been performed so far. Similar to MPH, the literature is not consistent about potential enhancement effects in neural processes. Furthermore, MOD's mode of action shows a diverse, task-dependent pattern (Table 2). In line with pharmacological findings, MOD effects were found in areas associated with high density of DA and NA neurons, such as the striatum (Kim et al., 2014; Volkow et al., 2009) and the midbrain (Minzenberg, Watrous, Yoon, Ursu & Carter, 2008), respectively. Imaging studies investigating potential neuroenhancement effects in executive functions showed increased activations in bilateral pons as well as PFC (Minzenberg et al., 2008). Notably, pons was deactivated through MOD when no task was performed. While working memory tasks showed deactivations in the PFC (Rasetti et al., 2010), reversal learning was associated with drug-dependent increases in BOLD signal in bilateral ventral occipito-temporal cortex, lateral occipital cortex, and superior parietal regions, right inferior frontal and right middle frontal gyri (Ghahremani et al., 2011). In contrast, two studies on decision making and reversal learning could not identify any brain regions affected by MOD in healthy controls (Schmaal et al., 2013, 2014). Since MOD affected activity in the striatum, an area strongly related to reward and addiction (Hyman, Malenka, & Nestler, 2006), the question of interaction between drug and reward is a matter of interest. Whereas MOD did not ameliorate any effect during addiction stimuli perception in healthy controls (Goudriaan, Veltman, Van Den Brink, Dom, & Schmaal, 2013), it showed enhanced activation in the Ncl. accumbens (NAc) during reward processing (Funayama et al., 2014). However, this effect was significant just for the highest reward condition and could not be observed in whole brain analysis.

Findings in sensory processing are also inconsistent. Whereas the authors of an early study postulated a baseline-dependent MOD effect in overall activated voxels (Ellis et al., 1999), newer studies reported activations as well as deactivations caused by MOD during sensory tasks (Joo, Tae, Jung, & Hong, 2008; Minzenberg, Yoon, & Carter, 2011).

Similar to MPH, MOD's mode of action on the neural level seems strongly task-dependent and shows a pattern of activation and deactivation in various brain regions. From the previous literature of MOD enhancement, the question of effect in memory enhancement cannot be adequately answered solely from the literature.

Table 2. 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, Watrous, Yoon, Ursu, & Carter, 2008	21	fMRI	200 mg	Executive functioning	Task switching	Accuracy increase in low-performers, RT cost correlated to drug dose	*MOD>PLA* Deactivations in bilateral pons *MPH X Task* Activations in bilateral pons and PFC
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)
Schmaal et al., 2013	16	fMRI	200 mg	Response Inhibition	Stop-Signal-Task	RT decrease in Go Trials	No effect
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, Veltman,	16	fMRI	200 mg	Addiction	visual	No effect	No effect

Van Den Brink, Dom, & Schmaal, 2013					observation of cocaine Stimuli		
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, Tae, Jung, & Hong, 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, Yoon, & Carter, 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							
Kim et al., 2014	10	PET	200 mg/ 300 mg	-	-	-	Enhanced DAT binding in striatum
Cera, Tartaro, & Sensi, 2014	26	RS fMRI	100 mg	Resting	Resting state	-	Increased FC in putamen, left parahippocampus, left posterior insula and MCC

MeSH terms: modafinil AND imaging OR MRI OR fMRI OR PET OR SPECT, scanning pubmed database and scholar.google.com, inclusion of healthy adults, exclusion of subjects younger than 18 years and history or presence of mental and physical diseases, study publication dates between 1990 and December 2015, only publications in English language, MOD>PLA = main drug effect, MOD X Task = interaction between drug and task, RS = Resting state, l = left, r = right.

2.4 Caffeine

Caffeine (CAF, 1,3,7-trimethylxanthine) is a natural stimulant occurring in several plants and commonly consumed in tea, coffee and soft drinks. Not considered as a drug, CAF is the most frequently consumed stimulant on the globe (Ferré, 2008). The daily CAF intake per person in the United States is approximately around 240 mg – which roughly corresponds to two medium cups of coffees (Barone & Roberts, 1996). In addition to its recreational function, it is discussed as an off-label treatment in several neurological disorders (Rivera-Oliver & Díaz-Ríos, 2014).

Besides its peripheral effects, CAF centrally acts as a non-selective adenosine antagonist in the CNS in which it binds to adenosine receptors A_1, A_{2a}, A_{2b} and A_3 (Takahasi, 2008). Adenosine receptors occur in an augmented amount in the striatum where they are co-expressed with D_2 receptors. Through the CAF-induced antagonism of this receptor heteromerization, an upregulation of DA signalling in the putamen and ventral striatum is discussed (Volkow et al., 2015). This mechanism may account for the increased arousal, locomotor behaviour and neurostimulation after CAF intake (Ullrich et al., 2015).

Orally administered CAF is rapidly absorbed by 99% in the GI tract. It reaches a peak plasma concentration around 30 minutes after intake and is almost completely metabolized in the liver through the CYP1A2 enzyme. CAF is evenly distributed in all body tissue. Since there is no blood-brain-barrier limitation, CAF rapidly reaches the CNS where it binds to adenosine receptors. CAF is mostly excreted through the renal system. The plasma half life of CAF is 2.5 to 5 hours (Arnaud, 2011).

Commonly consumed in moderate doses, CAF does not produce any health restricting side effects. Hallucinations may occur at doses from 1000 mg per day and more. Lethal consequences appear possible at doses from 5000 mg and more per day (Bramstedt, 2007). In addition to a homeostatic impact, CAF broadly affected cognitive functions such as sleep, attention and memory (Ullrich et al., 2015). Primarily increasing alertness, CAF reduced fatigue, boosted vigilance and improved simple motor reactions. These enhancement effects became more pronounced when subjects were sleep-deprived or lowered in alertness (Smith, 2002).

Several studies tried to answer whether CAF might be used for NE, exceeding the effect of light arousal enhancement. From an early study, potential NE effects were reported for motor activity, while other cognitive domains including verbal learning did not show any improvements (Rapoport et al., 1981). Notably, drug-naïve children showed greater

benefit from CAF than both groups of low vs. high CAF consuming adults. Before testing for CAF effects of a 3 mg/kg or 10mg/kg dose, all subjects were withdrawn for 3 days. This design, similar to other studies on CAF effects, was criticised by Rogers & Dernoncourt (1998) who postulated that mood and performance stimulating effects result partly from the relief of withdrawal. Consequently, the metabolism lacks the natural supply and works suboptimally. CAF corrects this imbalance and therefore leads to better performance. Newer findings on CAF abuse and addiction further supported this view (Juliano & Griffiths, 2004).

Summarizing previous CAF data on NE effects, Nehlig (2010) reported positive effects for arousal, mood and concentration. In contrast, performance in memory tasks was usually not affected by CAF intake. Working memory could get enhanced if the cognitive task load stayed simple. However, there were no positive findings on the effect of CAF in more difficult working memory tasks or long-term memory paradigms. A recent study using a single-dose application post-study design reported positive effects only for memory consolidation but not retrieval (Borota et al., 2014). This result suggests that time of intake as well as dosage, task characteristics and consumer habits influence a potential NE effect. Exploring constant CAF consumption, there were findings that report positive effects for long-term memory without interfering with other cognitive functions (Hameleers et al., 2000).

Besides neural activation changes, there were indications for CAF-induced vasoactive alterations (Laurienti et al., 2003). It seems that CAF reduced the cerebral blood flow (CBF) in general. While neural activity is associated with A_1 receptor antagonism, the blockage of A_2 receptors is thought to decrease CBF (Koppelstaetter et al., 2010). So far, it is not clear if the two effects interact with each other or occur independently of each other (Koppelstaetter et al., 2010). The expectation that CAF may act as a BOLD contrast enhancer through CBF reductions during baseline resting could not be fulfilled by any means (Laurienti et al., 2003). Basic research showed that the relationship between CAF, BOLD and CBF seems to be more complex than previously assumed (Mulderink, Gitelman, Mesulam, & Parrish, 2002; Bendlin, Trouard, & Ryan, 2007). So far, there are just a few studies using a demanding cognitive paradigm during imaging (Table 3). The authors of two fMRI studies on working memory in young healthy adults showed that CAF activated areas associated with attentional and executive functioning networks such as mediofrontal and cingulate cortex (Koppelstaetter et al., 2008). Controlled for the “withdrawal relief effect”, Klaassen et al. (2013) conducted another learning

experiment in fMRI. They confirmed prior findings of prefrontal activation for working memory encoding, but not for retrieval. Taken together, those two studies showed that caffeine may stimulate the fronto-parietal network which plays a key role in attention and also memory retrieval (Fox et al., 2005).

Table 3. 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, Hinrichs, Heinze, & Zaehle, 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, Gitelman, Mesulam, & Parrish, 2002	18	fMRI	200 mg	Sensory function	Checkerboard observation and finger movements	No effect	*BOLD Signal change CAF>Baseline* 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 subjects
Perthen, Lansing, Liau, Liu, & Buxton, 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, Perthen, & Liu, 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 & 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, Adan, Falcón, & Bargalló, 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	Finger tapping Checkerboard	Oddball: less missed responses, no effect	*CAF X Visual Task* Reductions in V1 and superior temporal lobe (l)

				Acoustic attention	Auditory oddball task	on false alarms or RT	*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, Trouard, & Ryan, 2007	21	fMRI	~ 222 mg	Novelty processing alertness	Word stem completion task	No effect	No effect
Resting State[1]							
Wu, Lien, Chang, & Yang, 2014	17	RS fMRI	200 mg	Resting state	-	-	CAF decreases FC in motor cortex and visual cortex, no difference for DMN

MeSH terms: caffeine AND imaging OR MRI OR fMRI OR PET OR SPECT, scanning pubmed database and scholar.google.com, inclusion of healthy adults, exclusion of subjects younger than 18 years and history or presence of mental and physical diseases, study publication dates between 1990 and December 2015, only publications in English language, CAF>PLA = main drug effect, CAF X Task = interaction between drug and task, RS = Resting state, FC = Functional Connectivity, NIRS = near infrared spectroscopy, HbO = oxyhemoglobin, HbR = deoxyhemoglobin, [1] example of an RS study, inclusion of all RS studies on CAF would have exceeded the review, l = left, r = right.

3. Hypotheses

In this study, subjects' performance in a 72-word list paradigm is tested. With prior memory studies taken into account, the chosen stimulants are likely to affect the DA system and therefore promote memory encoding as well as retrieval. From our functional data, we expect activation in prefrontal, striatal and hippocampal areas.

H1: Drug application of MPH, MOD and CAF leads to better performances in a declarative memory task compared to placebo.

H2: Subjects under MPH, MOD and CAF show enhanced wakefulness through improved reaction times compared to placebo.

H3: Subjects with lower baseline scores in fluid intelligence tests, attention and memory batteries benefit more from drug treatment than from placebo.

H4: Subjects with higher baseline scores in impulsivity questionnaires benefit more from MPH treatment than from placebo.

H5: During encoding task, the BOLD response is higher in the hippocampus of the drug groups compared to placebo.

H6: fMRI data during recall show higher activation in prefrontal and striatal areas in subjects during MPH, MOD and CAF treatment compared to placebo treatment.

4. Methods

4.1 Sample

After medical and mental pre-screening, a total of 48 healthy male volunteers were included in the study (age range = 21 – 36 years, *M* = 26.27, *SD* = 3.47). Women were deliberately not recruited due to proposed interaction of the female hormone cycle and brain function in memory-related brain areas (Lisofsky et al., 2015). All subjects were non-smokers and non-drug-addicted right-handers (Edinburgh Handedness Inventory Score, Oldfield, 1971: *M* = 84.0, *SD* = 20.0), who were recruited by means of online advertisement and flyers (Table 4). None of the subjects was on a diet, nor engaged in shift work. None of the subjects consumed coffee on a regular basis. Written informed consent was obtained from all participants.

Table 4. Demographic details of subjects

	MPH (*n* = 16)		MOD (*n* = 16)		CAF (*n* = 16)		Total (*n* = 48)	
Age (years)	25.8	(3.8)	26.6	(3.8)	26.4	(2.9)	26.3	(3.5)
Education (years)	15.7	(1.9)	17.0	(3.4)	16.7	(2.6)	16.5	(2.7)
EHI Score[1]	91.2	(12.6)	75.4	(26.6)	85.8	(15.8)	84.0	(20.0)
BMI[2]	23.3	(3.7)	23.4	(3.1)	22.5	(2.6)	23.1	(3.1)
Drug dose (mg/Kg)	0.27	(.04)	2.56	(0.34)	2.6	(0.32)		
Sleep per night (h)	8.2	(1.0)	8.0	(1.1)	7.8	(1.0)	8.0	(1.1)

Results are mean (SD). [1] EHI, Edinburgh Handedness Inventory (Oldfield, 1971). [2] Body mass index.

Exclusion criteria were history or presence of mental or physical disorders as determined through medical examination by a physician (D. R.), Beck Depression Inventory (BDI-V, Schmitt et al., 2006) and the SKID questionnaire (Strukturiertes Klinisches Interview für DSM-IV, Wittchen, Wunderlich, Gruschwitz & Zaudig, 1997). Intelligence was assessed using a measure of fluid intelligence, a German version of the Cultural Fair Test (CFT-20R; Weiss, 2006) as well as the digit-symbol-substitution-test (DSST, Wechsler, 1958). In addition, we administered a multiple choice lexicon intelligence test (Mehrfachwahl-Wortschatz-Intelligenz-Test (MWT), Lehrl, 2005) to assess crystallized intelligence. ADHD screening was assessed by means of a checklist of ADHD symptoms (Diagnostische Checkliste zur ADHS; Rösler et al., 2008) and the WURS-K questionnaire (Retz-Junginger et al., 2002). None of the subjects exceeded the cut-off score of 30 in either of the two tests and thus nobody was excluded based on ADHD screening. Memory performance outside the scanner environment was measured using a learning and memory test called Lern-und Gedächtnistest 3 (LGT; Bäumler, 1974), consisting of six subtests that assess three different memory domains: figural, verbal and numerical memory performance. In addition, we tested short-term memory

span using a long digit number that had to be recalled after an interval of 5 minutes ("numbers"). Data is summarized in Table 5.

In a cardiovascular examination, heart rate and blood pressure data were collected and a cardiogram (ECG) was recorded. Due to the magnetic field of the MR Scanner, all metal objects such as piercings had to be removed by the participants prior to scanning. For participation, all subjects were paid 100 €. The study was approved by the ethics committee at the Charité - Universitätsmedizin Berlin.

Table 5. Cognitive and mental assessment

	MPH (*n* = 16)		MOD (*n* = 16)		CAF (*n* = 16)		Total (*n* = 48)	
Mental Status								
ADHS-Checkliste	2.3	(2.7)	4.3	(4.7)	3.8	(5.4)	3.5	(4.4)
BDI-V	13.7	(8.6)	12.8	(9.8)	11.9	(8.9)	12.8	(8.9)
WURS-K	13.8	(9.1)	11.2	(9.2)	12.1	(9.4)	12.2	(9.1)
Memory								
LGT-3 – verbal memory	43.4	(8.0)	43.3	(5.3)	46.7	(6.9)	44.1	(6.8)
LGT-3 – figural memory	31.9	(6.1)	30.9	(4.8)	33.6	(10.9)	32.2	(7.6)
LGT-3 – memory standard	89.3	(15.9)	88.9	(12.4)	89.9	(14.4)	89.4	(14.0)
numbers	17.4	(11.6)	15.1	(9.9)	11.3	(9.0)	14.6	(10.3)
Performance								
CFT-20R Subtest 1	13.3	(1.8)	13.6	(0.9)	12.7	(1.8)	13.2	(1.6)
CFT-20R Subtest 2	11.7	(2.0)	11.5	(1.2)	10.6	(2.6)	11.3	(2.0)
CFT-20R Subtest 3	11.1	(2.4)	11.6	(1.8)	11.1	(2.2)	11.3	(2.1)
CFT-20R Subtest 4	7.3	(1.4)	7.3	(2.0)	7.8	(1.3)	7.5	(1.6)
DSST	41.1	(6.5)	36.9	(11.5)	32.7	(15.5)	36.9	(12.0)
MWT	28.3	5.2	28.2	(4.7)	28.2	(4.5)	28.3	(4.7)

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

All subjects' cardiovascular data as well as cognitive test batteries were assessed (N = 48). Six subjects were excluded from memory task analysis due to technical problems during imaging (3 in MPH, 2 in MOD and 1 in CAF) leading to 42 complete datasets of behavioral assessments. Furthermore, two subjects of the MOD and one subject of the CAF group had been dismissed from imaging analysis due to head movements that exceeded 3 mm, that correspond to a voxel diameter of a functional scan. In total, complete behavioral and imaging data was provided by 39 subjects (MPH = 13, MOD = 12, CAF = 14). Only vital signs were examined for all 48 subjects.

4.2 Design

The study was conducted in a double-blind 3-way crossover design alternating placebo and single-drug administration. Prior to drug sessions, all subjects underwent an initial assessment of behavioral assessment as well as cardiovascular, physical and mental examination. Randomly starting with placebo or drug, subjects were scanned twice with fMRI, which exactly seven days passing between the two sessions. Furthermore, a

number of subjective scales on cognition, mood and performance were administered during both sessions (not reported in the present thesis). Each subject received the placebo (microcrystalline cellulose) or one of the three treatments including 20 mg methylphenidate (Methylphenidat Hexal®), 200 mg modafinil (Vigil®) or 200 mg caffeine (Coffeinum®) during one session and vice versa during the second one (Figure 1). To match the fMRI period with maximal plasma concentration (C_{max}), subjects received the drug orally 90 min prior to scanning. 90 minutes appeared to be the adequate mean time comprising the three different drugs' peak plasma concentration. At both sessions, subjects were handed a white drug capsule with a glass of water. In order to avoid any possible pharmacological interference with food intake, all participants were requested to arrive sober without having eaten for 3 hours prior to the start of the experiment. Subjects were monitored for heart rate and for systolic and diastolic blood pressure during all phases of the experiment. To accustom to the scanning conditions, subjects were set up in the MRI scanner 15 minutes prior to functional imaging, while we acquired the localizer, the structural scan and a resting state scan. 24 hours after each session, subjects were contacted again to check their health status and collect late free recall performance data on the declarative memory task that was run during fMRI data collection.

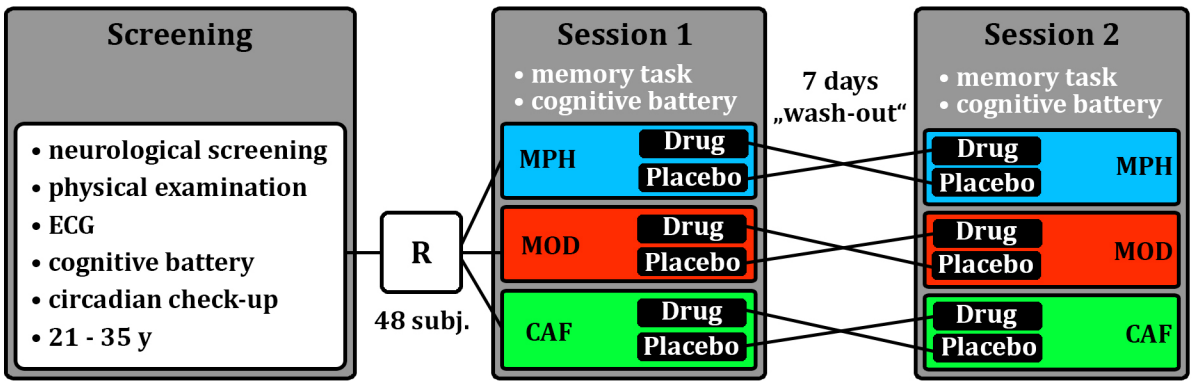

Figure 1. Study design. Initially, 48 subjects were included, later we had to discard 9 datasets due to data loss or head movement. Subjects were randomly assigned to one of the three treatment groups (MPH, MOD or CAF). Subjects started either with a placebo or a drug and the design was double-blind. In a second session after a 7 days wash-out period, the other substance was administered.

4.3 Procedure

Imaging was performed on a Siemens 3T Magnetom Trio Scanner (Siemens Healthcare, Erlangen, Germany) using an echo planar protocol with a 12-channel head coil. Positioned head first and supine in the magnet tube, subjects received visual stimuli of the memory paradigm via video goggles (VisuaStimDigital by Resonance Technology

Company Inc, CA, United States). Functional images were acquired in the axial plane using a T2* weighted echo planar imaging (EPI) sequences (Time of Repetition (TR) = 2000 ms; Time of Echo (TE) = 30 ms, image matrix = 72 x 72, Field of View (FoV) = 216 mm, flip angle = 80°, slice thickness = 3 mm, distance factor = 20%, voxel size = 3 x 3 x 3 mm). On each day, subjects could independently pace their response in fMRI, hence the time series vary in their number of volumes between trials and subjects. For fMRI coregistration, 192 high-resolution T1 weighted 3D MPRAGE whole-brain images were recorded (TE = 4.77 ms, TR = 2500 ms, image matrix = 256 x 256, FoV = 256 mm, flip angle = 7°, slice thickness = 1 mm, voxel size = 1 x 1 x 1 mm).

Prior to scanning, subjects were orally instructed how to perform both parts of the declarative memory task and asked to describe the procedure in their own words to ensure correct understanding of the task. At first, subjects underwent the learning paradigm where they had to learn the order of 72 words. In each of 12 blocks six words were presented (shown for 3 seconds each). Between each block, subjects had a break of 25 seconds to relax (Figure 2). Word lists with at least 70 words prevent ceiling effects and therefore seem to be an adequate choice for healthy young subjects (Riedel & Blokland, 2015).

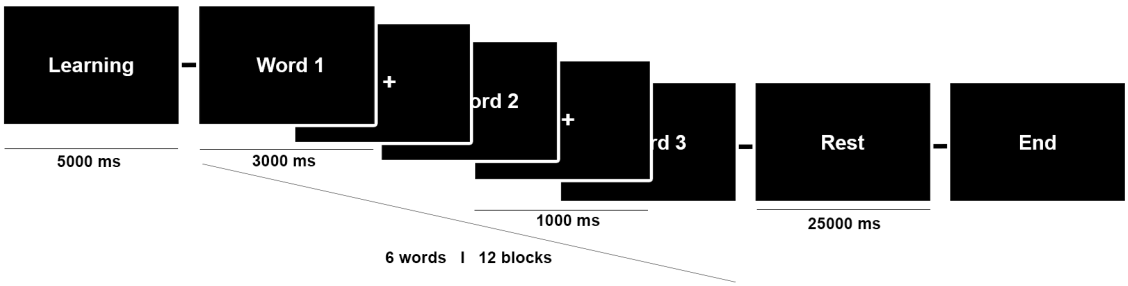

Figure 2. Learning task in fMRI. In 12 blocks separated by 25 seconds resting intervals, subjects were instructed to memorize a total of 72 words. All random German words appeared in white font on black background. At each test session, different word lists were used. A list of the word pool of each session is provided in supplementary material.

Immediately after the learning task, a recall task was performed within the MRI scanner to measure declarative memory retrieval. Participants had to judge whether the presented word order corresponded to the order seen before (Figure 3). As a neutral control condition, subjects were asked to count syllables of random word sequences. Additionally, median reaction time and confidence judgement of all responses were assessed.

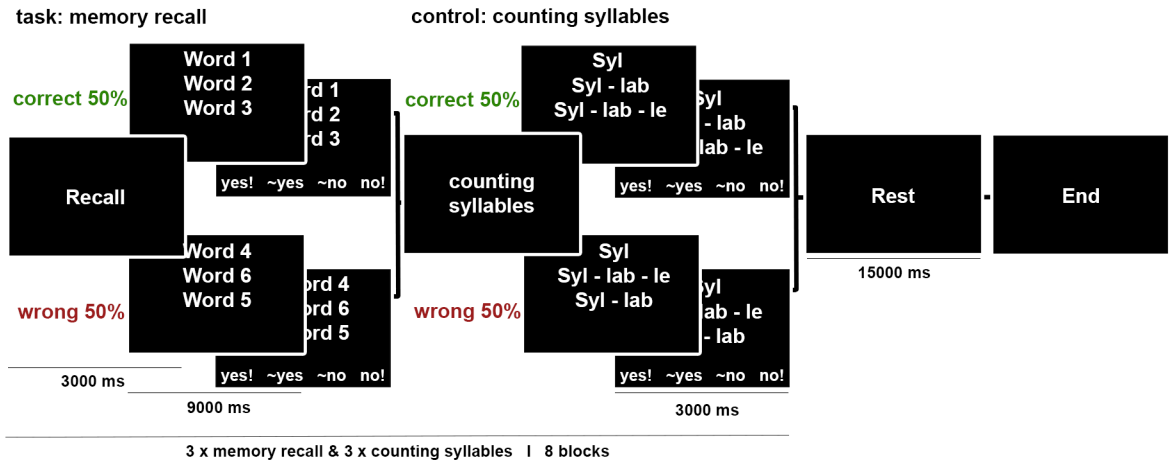

Figure 3. Recall task in fMRI. Subjects judged three simultaneously presented words whether they were in the same order as presented during the prior learning phase. Controlling for visual and semantic stimulation, subjects had to decide about the rising syllable length of a row of three words in a control condition ("counting syllables"). In randomized order, memory and control tasks were presented during eight blocks. Subjects were required to indicate, by pressing a button, whether the words were correctly presented and how certain they felt about it ("yes!", "~yes", "~no", „no!"). Each task was introduced by an instruction screen lasting 3000 ms. Word lists were presented for 9000 ms, whereas decision time was restricted to 3000 ms. After each block, a brief delay of 15 seconds gave subjects time to relax. All screens were displayed in white font and black background. The measure of performance used was the total number of correct responses as well as reaction time (RT) of responses.

For behavioural analysis, SPSS (IBM® SPSS® Statistics 22.0, 64-Bit-Version, http://www-01.ibm.com/software/de/analytics/spss/) was used. For the recall task, subjects had to judge whether the order of words was correct or wrong (direct word order judgement). Performance in the word order judgement task was defined as the total number of correct responses, consisting of the correct acceptance of a presentation of correct order as well as the correct rejection of the presentation of a wrong order. To correct for any bias of very slow responses that were not recorded due to a given response window of 3000 ms, all data was corrected for response misses ([correct responses / total responded items] * all possible items). During every item, three words were presented on top of each other. In total 24 task items could be possibly correctly answered. Control task responses were used as a control of motivation and effort. Here, all participants had a performance above 90% correct trials. Likewise, subjects could deal with 24 items at most. Moreover, subjects were able to indicate their confidence during recall and control task about the correct likelihood of their response (high vs. low confident). In the result section, the confidence measure is reported as the percentage of high confident responses of all given responses. Since unconfident responses were rarely reported, this behavioral dimension was not integrated into imaging data. Parallel to the correctness of responses, reaction times (median) of subjects were assessed. Immediately after scanning, subjects were asked to recall as many words of the memory task as possible ("early free recall"). The day after testing, all subjects were called on the

phone to recapitulate all words of the memory task again ("late free recall"). During both, early and late free recall, subjects could possibly recall a total of 72 words. Commission errors, i.e. items that were not part of the word list, were not counted. Furthermore, the body weight-adjusted drug doses for each participant were calculated and correlated to behavioral performance. Physiological and behavioural measures were analysed separately using repeated-measures analysis of variance (ANOVA) to isolate the drug effect of each enhancer group. The within-factor in the ANOVA was the treatment condition (drug or placebo) and the between-factor was the enhancer group (MPH, MOD, CAF). To further assess the time course of physiological parameters, an additional within-factor time (baseline/ 120minutes/ 240 minutes) was included. As dependent variables, several behavioral and physiological measures were examined (i.e. correct responses during early recall). After the ANOVA, post-hoc two-tailed paired t-tests were also applied.

Imaging data was analysed with Statistical Parameter Mapping 12 (SPM12, Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk/spm). The imaging task was scripted and analysed with Presentation® (Neurobehavioral Systems, Inc., http://www.neurobs.com/). First, all images of each subject were corrected for slice timing and realignment. For the next preprocessing 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, Montreal, Canada). Movement data exceeding 3mm translation on the x-, y-, or z-axis or 3° rotation was excluded from further analysis. For normalization, a unified segmentation was used to classify anatomical T1-weighted images into grey 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, 128s).

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 either for the learning and recall task, respectively. Additionally, movement parameters as well as model constants were implemented. For the learning task, the contrasts between learning and resting (Learning>Resting and Resting>Learning) were computed, whereas learning items were recorded as events and the resting condition consisted of a block of 25 s duration. The following were selected as the main regressors

of interest of the recall task: (1) correct task response during drug, (2) correct control response during drug, (3) correct task response during placebo, (4) correct control response during placebo. In the first level analysis in the recall task, neural activity correlates at correct retrieval were contrasted to items that were correctly processed during control condition (Task_correct>Control_correct and Control_correct >Task_correct).

On the second level, contrast maps from single-subject analysis were used to contrast drug with placebo effects within the learning and recall task. Three independent enhancer groups were created (MPH>PLA, MOD>PLA, CAF>PLA). Unless otherwise indicated, statistical values of the whole brain analysis were thresholded at a significance level of $p < .001$ (uncorrected). From Monte Carlo simulation-based cluster size correction, a significant effect corresponding an alpha error probability of $p < 0.05$ can be assumed when the volume exceeded the minimum cluster size of 22 voxels (AlphaSim, Song et al., 2011). MNI coordinates of activated areas were assigned to brain regions using the SPM function "Neuromorphometrics" (Neuromorphometrics, Inc., http://Neuromorpho-metrics.com/) as well as the Anatomy toolbox (Eickhoff et al., 2005) and WFU Pickatlas (Tzourio-Mazoyer et al., 2002).

To investigate certain brain areas in a hypothesis-driven manner, the drug effects were also assessed using small volume correction limited to an anatomic mask including the bilateral PFC, bilateral parahippocampal gyrus and bilateral hippocampus defined a priori in the WFU Pickatlas (Tzourio-Mazoyer et al., 2002). Here, statistical significance for the regions-of-interests were defined at the voxel level ($p < .05$) corrected for multiple comparisons. The analysis was performed using the SPM toolbox MarsBaR (Brett, Anton, Valabregue & Poline et al., 2002). Then, regions revealing significant effects of certain drugs were correlated with performance measures as well as individual 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.

5. Results

5.1 Physiological data

For heart rate (HR), systolic blood pressure (RR_{sys}) and diastolic blood pressure (RR_{dia}) three separated repeated-measures ANOVAS were performed using time passed after drug application (0/120/240 min) and treatment (drug/placebo) as within-subject factors and enhancer group (MPH/MOD/CAF) as the between-subject factor. For heart rate, there was a significant effect for time ($F_{(2,90)} = 17.96$, $p < .001$), treatment ($F_{(1,45)} = 8.8$, $p < .01$) and enhancer group ($F_{(2,45)} = 3.47$, $p < .05$) as well as for the interaction time X treatment X enhancer type ($F_{(4,90)} = 3.07$, $p < .05$). For RR_{sys}, there was a similar main effect for treatment ($F_{(1,45)} = 9.78$, $p < .01$). For RR_{dia}, the ANOVA revealed a significant main effect for time ($F_{(2,90)} = 12.13$, $p < .01$) as well as for the interaction treatment X time X enhancer type ($F_{(4,90)} = 2.83$, $p < .05$).

In a second step, the different time points of HR, RR_{sys} and RR_{dia} were subtracted from baseline measure. For HR (Figure 4A), post-hoc paired t-tests revealed a significant drug–placebo difference only for MPH after 120 min (mean paired difference, 6.2 bpm, $p < .01$) and 240 min (mean paired difference, 10.6 bpm, $p < .01$). Similarly, blood pressure increased over time course (Figure 4B,C). RR_{sys} was significantly increased under MPH compared to placebo after 120 minutes (mean paired difference, 8.6 mmHg, $p < .05$), but not after 240 minutes ($p > .12$). Furthermore, MPH led to an increase in RR_{dia} after 120 minutes (mean paired difference, 5.3 mmHg, $p < .05$) and 240 minutes (mean paired difference, 8.3 mmHg, $p < .05$) compared to placebo. For CAF and MOD, post-hoc analysis could not reveal any difference between drug and placebo for any of the vital signs ($p > .21$). For none of the stimuli groups were a dose-dependent (mg / kg body weight) effect found in the physiological data.

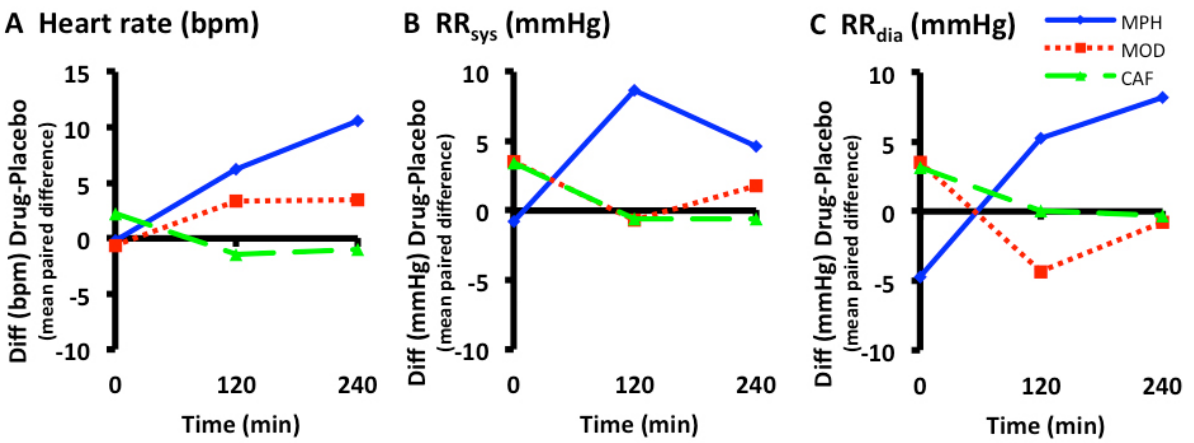

Figure 4. Cardiovascular data ($N_{Total} = 48$, $N_{Group} = 16$). (A) Heart rate, (B) systolic blood pressure, (C) diastolic blood pressure, drug-placebo difference over time.

5.2 Behavioural data

5.2.1 Main effects

Two repeated-measures 3 X 2 ANOVA with the between-subject factor enhancer group (MPH/MOD/CAF) and within-subject factor treatment (drug/placebo) were performed to assess direct word order judgement as well as confidence. Amount of correct word order responses and percentage of high confidence were set as dependent variables. During direct word order judgement, no group difference ($F_{(2,39)}$ = .13, p > .88) and no treatment effect was revealed ($F_{(1,39)}$ = .09, p > .77). Similarly, there was no group effect ($F_{(2,39)}$ = .87, p > .43) nor treatment effect ($F_{(1,39)}$ = 0.17., p > .67) for task confidence ratings. However, a post-hoc paired t-test revealed a higher ratio of high-confident task responses of subjects during MPH (M = .79, SD = .16) compared to placebo (M = .68, SD = .22), $t_{(12)}$ = 2.46, p < .05, but not in the other enhancer groups (p > . 67).

To assess early and late free recall, a repeated-measures ANOVA was performed with the between-subject factor enhancer group (MPH/MOD/CAF) and the within-subject factors recall (early/late) and treatment (drug/placebo). The number of freely recalled words was used as a dependent variable. The main effects recall ($F_{(1,39)}$ = 123.25, p < .001) and treatment ($F_{(1,39)}$ = 7.23, p < .05) were significant. No difference was found for enhancer group (p > .91). For early recall post-hoc paired t-tests revealed a trend in MPH towards improved memory retrieval (M = 36.62, SD = 14.78) compared to placebo (M = 29.69, SD = 14.09), $t_{(12)}$ = 2.14, p = .053, whereas CAF (M = 34.87, SD = 22.99) vs. PLA (M = 33.07, SD = 21.7), $t_{(14)}$ = .67, p > .52, and MOD (M = 30.79, SD = 16.03) vs. PLA (M = 29.86, SD = 14.01), $t_{(11)}$ = .42, p > .68, did not differ significantly. The late recall assessment revealed a significant higher amount of correctly recalled words in MPH (M = 19.54, SD = 8.9) compared to the placebo condition (M = 13.23, SD = 8.56), $t_{(12)}$ = 3.89, p < .01 (Figure 5). No significant difference in late free recall was found for CAF (M = 22.73, SD = 24.26) vs. PLA (M = 16.07, SD = 12.09), $t_{(14)}$ = 1.24, and MOD (M = 20.14, SD = 17.51) vs. PLA (M = 17.14, SD = 15.49), $t_{(13)}$ = 1.25, both p > .24.

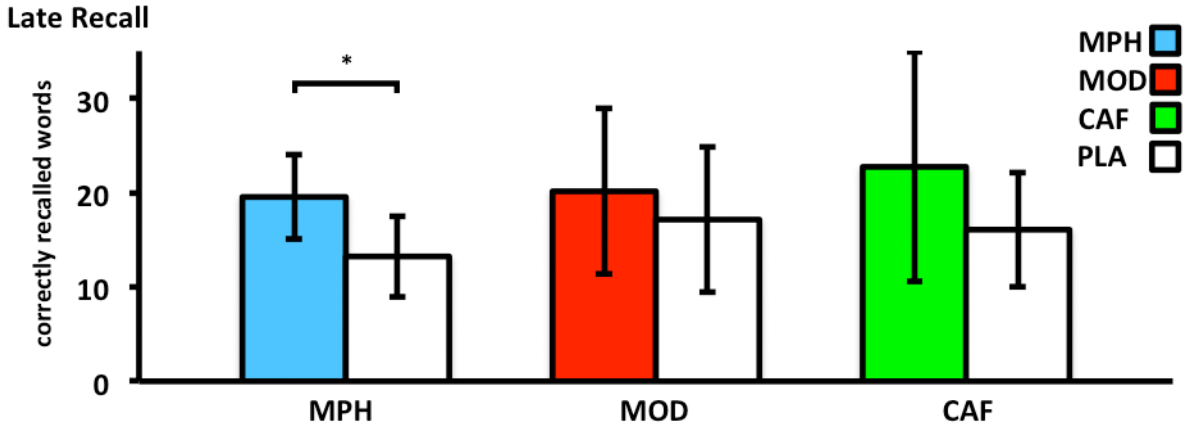

Figure 5. Late free recall performance. Box plot of the three drug groups compared to placebo administrations. Subjects significantly recalled more words during MPH application compared to placebo (PLA), * $p < .01$. Bars represent standard deviations.

For MPH and MOD, no relationship was seen between drug-induced differences in correct word order, confidence, early and late free recall (all $p > .09$). For CAF, a relationship was found between confidence and memory task performance ($r = .53$, $p < .05$) as well as early ($r = .74$, $p < .01$) but not delayed recall ($p > .12$). However, task performance correlated with both early ($r = .64$, $p < .05$) and late free recall ($r = .62$, $p < .05$). The amount of drug concentration was equal for all subjects of each group. Corrected for body weight, the individual drug dose per body weight (mg/kg) could be estimated. In order to evaluate whether each drug enhanced memory performance, correct responses in direct order task, early and late free recall on placebo were subtracted from those specific for each drug. We did not find any significant dose-performance or dose-confidence correlation for any drug ($p > .1$).

5.2.2 Task and physiology Interactions

In the MPH group, $RR_{dia,120}$, $RR_{dia,240}$ and $RR_{sys,240}$ positively correlated to confidence during memory task ($r = .62$, $r = .65$ and $r = .56$, respectively). Furthermore, $RR_{dia,120}$ but not $RR_{dia,240}$, negatively correlated with the amount of correct responses during the memory task ($r = .64$), all $p < .05$. No other relationship between performance, confidence and neither heart rate, nor administered dose (mg/kg) could be established within the MPH group ($p > .08$). Subjects' performance increase during CAF in late free recall correlated negatively to $RR_{dia,240}$ ($r = -.56$, $p < .05$). No other change in performance or confidence dependent on their physiological condition could be found ($p > .13$). During MOD, subjects' confidence increase after drug intake correlated to $RR_{sys,240}$ ($r = .65$). Furthermore, their HR_{120} correlated to early free recall performance ($r = .54$), all $p < .05$, whereas the other performance or confidence measures of the MOD group did not correlate to any vital sign ($p > .14$).

5.2.3 Reaction times

A repeated-measures 3 X 2 ANOVA with treatment group (MPH/MOD/CAF) as the between-subject factor and treatment (drug/placebo) as the within-subject factor was performed to examine reaction times as a dependent variable. RTs of all task and control responses did not differ regarding group ($p > .053$) or treatment ($p = .05$). However, RT for task responses revealed a main effect for enhancer group ($F_{2,39} = 3.87$, $p < .05$). Moreover, the ANOVA for RT for correct task responses was significant for enhancer croup ($F_{2,39} = 3.25$, $p < .05$) as well as for the interaction enhancer group X treatment ($F_{2,39} = 4.37$, $p < .05$). RT for control task did not differ in any respect ($p > .05$). Post-hoc paired t-tests showed that within the CAF group, subjects responded slower for task responses under drug treatment than under placebo, $t_{(14)} = 2.64$, $p < .05$. This treatment difference was even more pronounced for correct task responses, $t_{(14)} = 3.24$, $p < .01$ (Table 6). However, the drug-associated slow acting was particular seen during task execution. There was no significant RT difference found for the control task between drug and placebo ($p > .59$). No treatment effect on RT could be revealed for both MPH and MOD ($p > .29$).

Subjects who were treated with MPH did not exhibit significant correlations between RT and drug-dose-concentration and task performance, respectively. In contrast, mean RT over all trials ($r = -.71$) and RT for correct task responses ($r = -.75$) correlated to high confidence during correct task responses in a negative manner, $p < .01$. The MOD subjects showed a slightly positive correlation between overall RT and drug-dose ($r = .54$) under drug treatment. Furthermore, their RT for correct responses correlated to their performance during late recall ($r = -.59$). Subjects who were administered CAF showed negative correlations between RT during correct task responses and drug-dose per body weight ($r = -.611$), correct responses ($r = -.68$), high confidence ($r = -.62$), high confidence during correct responses ($r = -.77$), correct early recall responses ($r = -.62$) as well as correct late recall responses ($r = -.52$). All correlations were significant under $p < .05$. No relationship between cardiovascular data and reaction times could be shown for any of the three treatment groups.

Table 6. Mean reaction times of drug groups

	MPH (n = 13)		MOD (n = 14)		CAF (n = 15)	
	Drug	Pla	Drug	Pla	Drug	Pla
Overall responses	.65 (.13)	.62 (.12)	.72 (.20)	.69 (.22)	.59 (.11)	.55 (.09)
Task responses	.72 (.18)	.73 (.18)	.79 (.22)	.80 (.27)	.67 (.19) *	.55 (.12)
Correct task responses	.70 (.17)	.72 (.19)	.76 (.21)	.79 (.28)	.69 (.19) **	.54 (.12)
Control responses	.60 (.11)	.57 (.13)	.66 (19)	.63 (.21)	.56 (.11)	.54 (.09)

Results are mean (SD), * $p < .05$, ** $p < .01$.

5.2.4 Cognitive scores and personality traits

Within the MPH group, high impulsivity scores in ADHD questionnaires (Wurs-k, ADHS Checkliste) correlated to performance benefit in late free recall under drug (r = .56 and r = .68, respectively, p < .05), but not to direct order judgement (p > .3). Furthermore, Wurs-k, but not ADHS Checkliste (p > .24), correlated to performance benefit in early free recall under MPH (r = .56, p < .05). No correlations were found for IQ Scales (CFT-20R, DSST), education (education years) or basic memory assessment (LGT, numbers) on performance in direct judgement and free recall, all p > .19. In the CAF group, subjects' performance benefit under drug in direct word order judgement (r = .57) as well as late recall (r = .6) correlated to their performance in the LGT subscale FG (=spatial memory), both at p < .05, but not in other subscales of the LGT or to other cognitive measures. MOD subjects' performance benefit through drug application in early free recall correlated negatively to one intelligence subscale (CFT-1, r = - .55, p < .05). Furthermore, their years of education correlated positively to late recall performance after drug administration (r = .57, p < .05). All other scales failed to reach significance (p > .07).

5.2.5 Order and learning effects

To identify order and learning effects, two repeated-measures ANOVAs were performed. First, an ANOVA with treatment (drug/ placebo) as within-subject factor and enhancer (MPH, MOD, CAF) and drug order (first enhancer/ first placebo) as the between-subject factors was performed. This showed no significant interaction neither with drug order X treatment nor with drug order X treatment X enhancer 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 (first enhancer/ first placebo) and enhancer group (MPH, MOD, CAF) as between-subject factors was performed. Likewise, there was no significant variance explained for day order nor for day order X enhancer type, day order X drug order or day order X enhancer type X drug order, all p > .17. Taken together, these results do not confirm any order or learning effects in the data.

5.3 Imaging data

5.3.1 Encoding

A whole-brain analysis was performed for the contrast Learning>Resting at a threshold set at p < .05, corrected for family-wise error (FWE). For Learning compared with resting baseline, significant and extensive activation was seen in widespread networks

bilateral in occipital lobe, gyrus parahippocampalis, SMA and left DLPFC across all subjects (Figure 6).

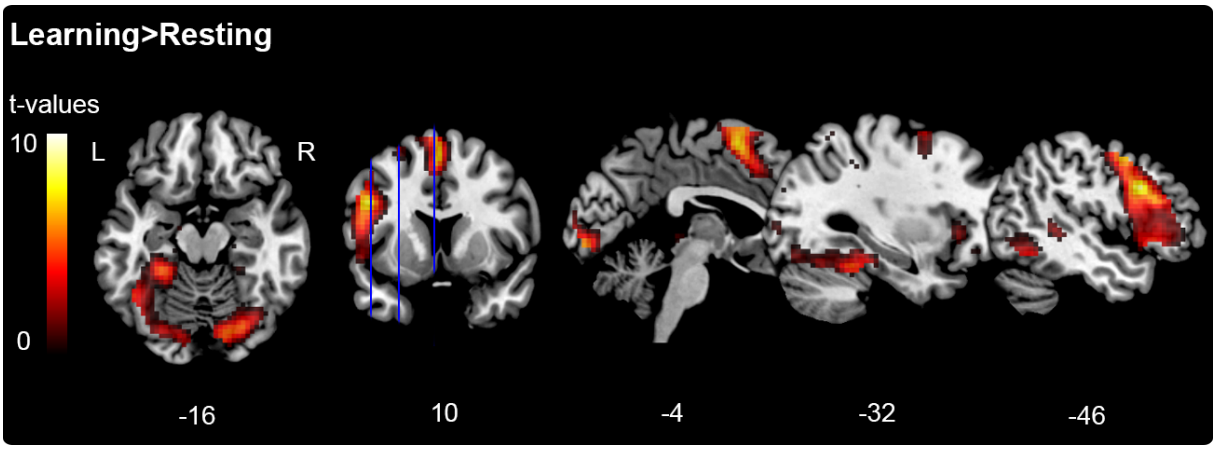

Figure 6. BOLD signal increase during encoding in 39 subjects. Contrast Learning>Resting in occipital, temporal and frontal areas. L = left, R = right. All Clusters > 22 voxels are shown, FWE corrected.

The opposite contrast Resting>Learning showed significant activations within the default mode network including prefrontal, parietal and temporo-insular areas. All findings are summarized in Table 7.

Table 7. Peak Voxels of activated clusters during learning and resting condition,

Region	BA	MNI coordinates			Laterality	*t*-score	K_E
		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), $K_E > 22$, N = 39; FWE = Family-wise error corrected, K_E = Cluster size, R = right, L = left

5.3.1.1 Drug effects

During Encoding, there was no significant main effect of MPH, MOD or CAF found on BOLD signal response for either condition. MPH and MOD neither activated nor deactivated signal in any brain during any interaction. However, the contrast Learning under placebo vs. Learning under drug within the CAF group showed enhanced BOLD signal bilateral in the precentral gyrus, medium segment (peak voxel: 0, -31, 62, $t_{(13)}$ = 5.53, cluster size of 24 voxels, p(unc.) < .001, BA4). Furthermore, the same region (peak

voxel: 0, -31, 62, $t_{(13)}$ = 6.5, cluster size of 50 voxels, p(unc.) < .001, 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, p(unc.) < .001, BA4) were deactivated for the interaction contrast Learning X CAF (CAF (Learning>Resting)>(Placebo>Drug)), Figure 7, Table 8.

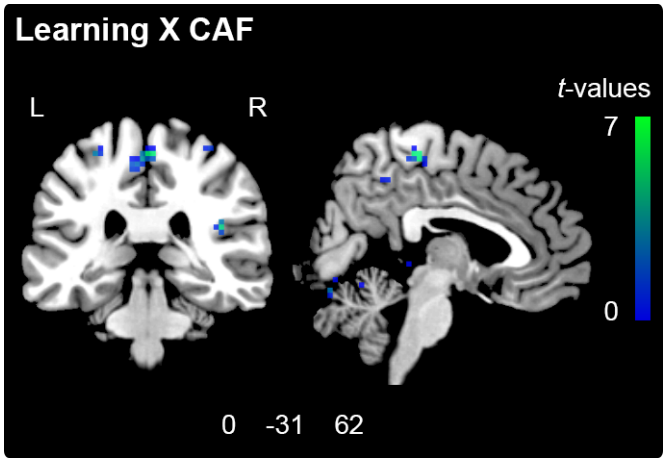

Figure 7. Contrast interaction for Learning X CAF (CAF (Learning>Resting)>(Placebo>Drug)) in precentral gyrus. L = left, R = right. All Clusters > 22 Voxels are shown, p < .001 (unc).

No deactivated region showed any correlation to performance measures or to cognitive scores. A trend was found for precentral gyrus signal activation and early recall (r = .52, p = .06), but not for delay recall (p = .1). The deactivation of BOLD signal in the parietal operculum did not correlate to any recorded data.

Table 8. Peak Voxels of activated clusters for the interaction learning and CAF

Region	BA	MNI coordinates			Laterality	*t*-score	K_E
		X	Y	Z			
Deactivations Learning X CAF							
Precentral gyrus	4	0	-31	62	R/L	6.50	50
Parietal operculum	40	-51	-10	20	L	6.33	35

BA = Brodmann's area , p < 0.01 (unc.), K_E > 22, N = 14

5.3.1.2 Region-of-Interest analysis

During learning, none of the drugs caused a difference in contrast estimates in hippocampus, parahippocampal gyrus or in the PFC, all p > .05 (Figure 8). The contrast estimates did not correlate to any cognitive or behavioral score.

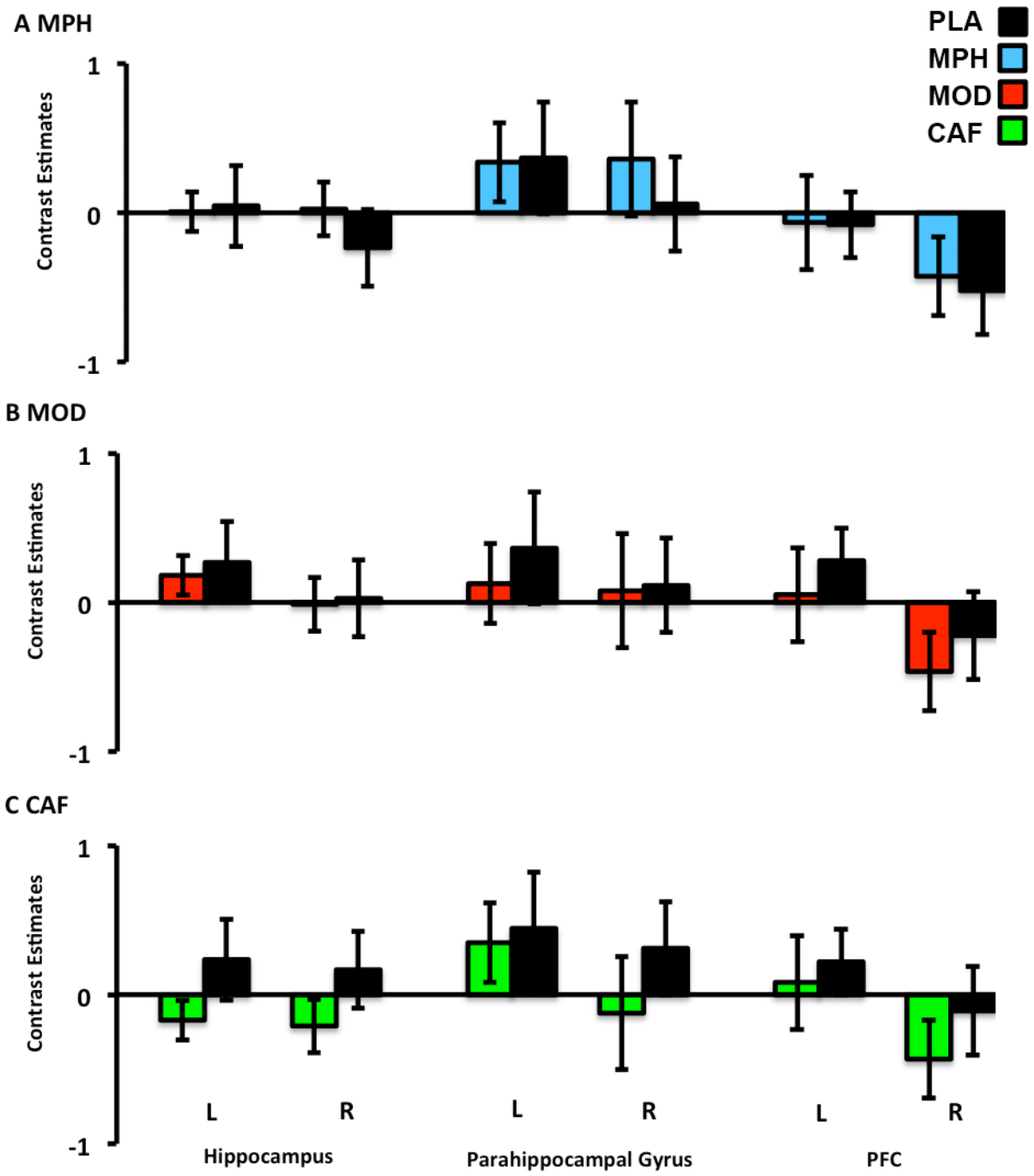

Figure 8. ROI analyses of hippocampus, parahippocampal gyrus and PFC for the contrast Learning>Resting.

5.3.2 Recall

To illustrate recall processing of all subjects, the BOLD signal during recall was contrasted with the control condition (p < .001, unc., clustersize > 22 Voxels). The within-subject comparison between recall and control condition revealed significant task-related activations in widespread cortical and subcortical networks including the parietal lobe, left frontal lobe and also bilateral occipital lobe. Furthermore, bilateral activations were found in the caudate nucleus, ACC and middle temporal regions (Table 9, Figure 9). On the other hand, Control>Recall revealed activations in ACC, gyrus

supramarginalis, precuneus, bilateral hippocampus, left insula, middle temporal gyrus and PCC.

Table 9. Peak Voxels of activated clusters during recall and control condition

Region	BA	MNI coordinates			Laterality	*t*-score	K_E
		X	Y	Z			
Recall>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>Recall							
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, $p < .001$ (unc.), $K_E > 22$, N = 39

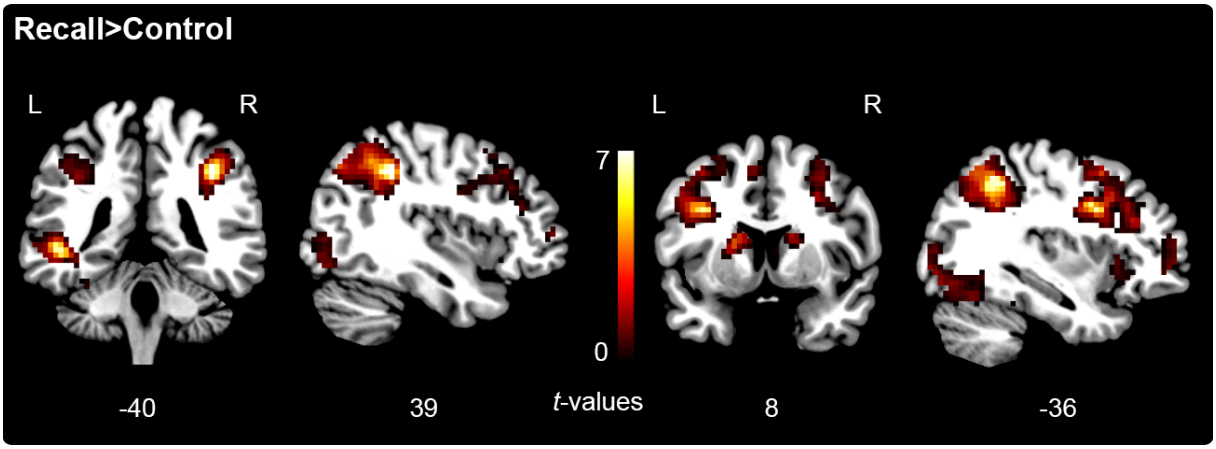

Figure 9. BOLD signal increase during recall in 39 subjects. Contrast Recall>Control in parietal, temporal and frontal areas. L = left, R = right. All Clusters > 22 Voxels are shown, p < .001 (unc.).

5.3.2.1 Drug effects

In the MPH group, the contrast Recall vs. Control showed significant activation at superior occipital gyrus when a placebo was given. However, this effect did not appear when the drug was given. Furthermore, MPH showed a significant interaction effect between drug and Recall. Deactivations were found in supplementary motor cortex, right middle temporal gyrus and left superior parietal lobules (Figure 10). No increased BOLD signal was found for the interaction Recall X drug.

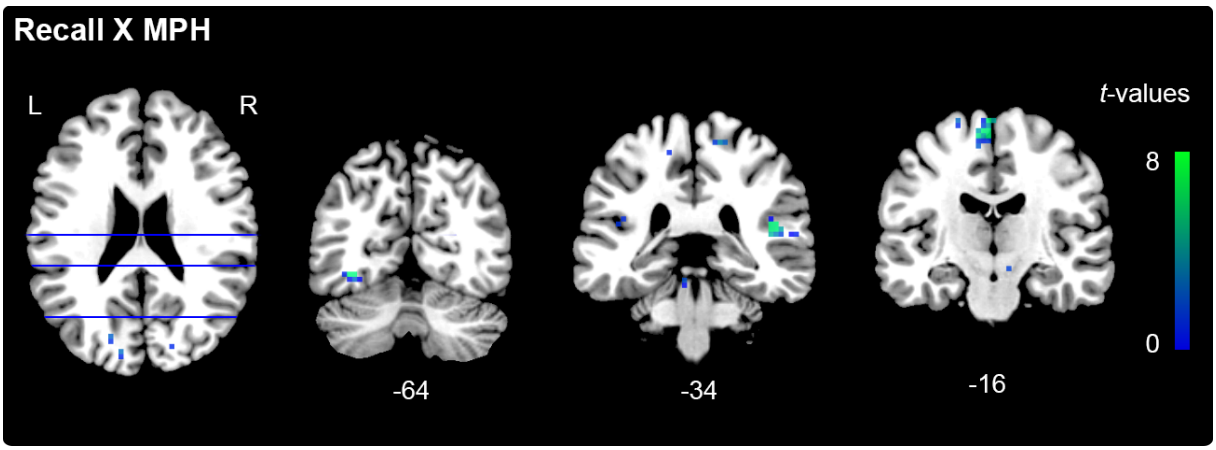

Figure 10. Contrast interaction for Recall X MPH (MPH (Recall>Control)>(Placebo>Drug)) in SMA, right superior temporal gyrus, left inferior occipital gyrus. L = left, R = right. All Clusters > 22 Voxels are shown, p < .001 (unc).

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 Recall as well as for the control condition (Figure 11A). During the control condition, voxels within the ROI appeared to be more strongly activated than during recall task, but did not show a significant difference, p > .09 (Figure 11B). Second, the contrasts of the Recall X MPH interaction were examined in particular. For this purpose, the beta weights of the single contrasts Drug_Recall>Baseline, Drug_Control>Baseline, Placebo_Recall>Baseline, Placebo_Control>Baseline were extracted for the ROI SMA. Further, the interaction of the two factors treatment (MPH vs. placebo) and task (recall vs. control) was calculated ($F_{(1,48)}$ = 10.29, p < .01). The graphic presentation reveals a bidirectional effect of the factor task during MPH but not during placebo (Figure 11C).

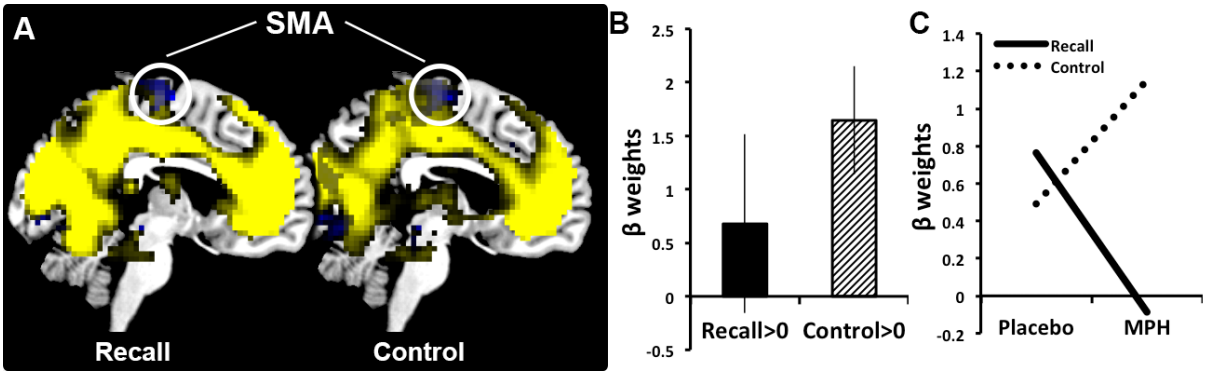

Figure 11. Extraction of the ROI SMA that was identified as one of the regions showing significant alterations for the interaction MPH X Recall. (A) Overlap of the ROI SMA (blue) and activated regions for the contrasts Recall>Baseline and Control>Baseline (yellow). (B) Comparison of grouped beta weights for the contrasts Recall>0 and Control>0, difference is not significant. (C) Plotted interaction of the extracted beta weights of the factors task and medical intervention.

Hence, the basis of the interaction contrast Recall X MPH is formed by either an increase of BOLD signal during control condition or a decrease during recall task, respectively. Subjects of the MOD group showed an activation pattern for the contrast Recall>Control when they were given a drug but not when given a placebo. Bilateral activations were found in the middle frontal gyrus, precuneus, left middle temporal lobe, supramarginal and occipital gyrus. In addition, no BOLD signal changes were shown for the contrasts Recall>Control for CAF subjects when they were given a drug or a placebo. A whole-brain analysis of the interaction between Recall and CAF and MOD, respectively, did not show any signal changes (Table 10).

Table 10. Peak Voxels of activated clusters under MPH and MOD

Region	BA	MNI coordinates			Laterality	*t*-score	K_E
		X	Y	Z			
Deactivations Task X MPH							
SMA	6	-6	-16	68	R/L	7.58	45
Superior temporal gyrus	41	48	-34	14	R	7.44	27
Inferior occipital gyrus	19	-36	-64	-7	L	6.58	22
Lingual Gyrus	18	-9	-73	-7	L	6.43	24
MPH Recall>Control during placebo							
Superior occipital gyrus	17	-15	-88	20	L	6.00	84
MOD Recall>Control during drug							
Middle frontal gyrus	6	30	14	50	R/L	8.75	31
Precuneus	7	-12	-61	44	L	7.10	270
Middle temporal gyrus	21	-54	-37	-10	L	6.37	26
Cerebellum		12	-73	-25	R	5.81	28
Inferior parietal sulcus	40	39	-40	38	R	5.76	48
Inferior occipital gyrus	18	-33	-88	-4	L	5.38	31

BA = Brodmann's area, $p < 0.01$ (unc.), $K_E > 22$, $N_{MPH} = 13$, $N_{MOD} = 12$

The deactivated areas of the MPH group during task assessment did not show any relationships to task performance, early and late recall or reaction times. However, the VOI analysis of the left lingual gyrus ($r = .61$) and the right superior temporal gyrus ($r = .76$) revealed a correlation with the applied MPH dose/ kg body weight. No such significant correlations were found for the SMA region or in the left occipital gyrus.

5.3.2.2 Region-of-Interest analyses

Likewise, in the prior learning phase, also during recall, subjects did not show any difference in contrast estimates between drug and placebo for any of the investigated regions, $p > .05$ (Figure 12).

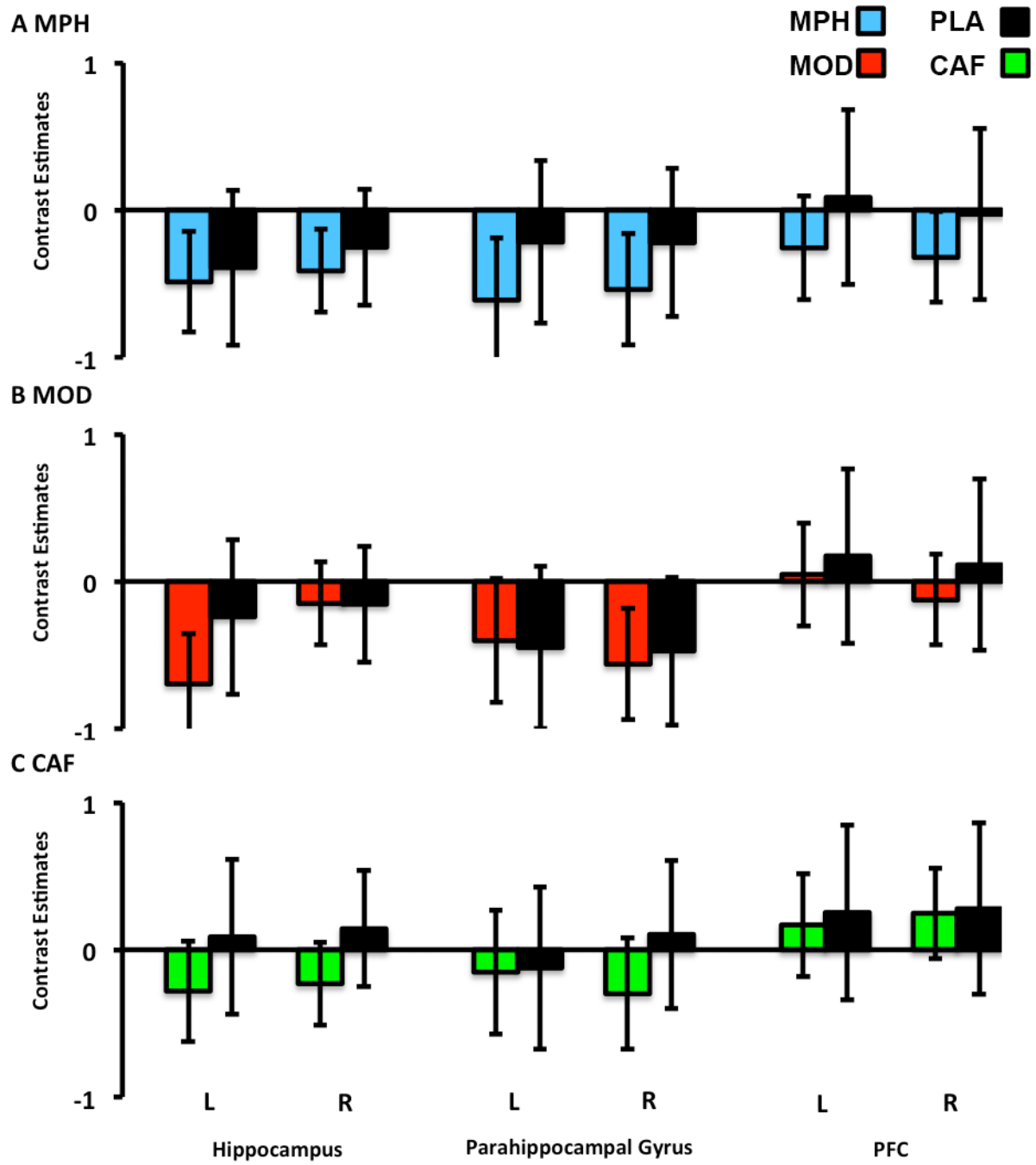

Figure 12. ROI analyses of hippocampus, parahippocampal gyrus and PFC for the contrast Recall>Control.

6. Discussion

In this study, the influence of methylphenidate, modafinil and caffeine on declarative memory function was investigated in healthy adults using functional imaging. At the behavioral level, MPH enhanced late free recall performance as well as judgement confidence. This enhancement positively correlated with ADHD scores collected during screening assessment; CAF prolonged RT during correct trials, whereas MOD did not reveal any effect at all. At the neural level, MPH administration led to decreases in BOLD signal in the SMA as well as small clusters in the temporo-occipital region during direct retrieval of a word sequence. No effect was found here for MOD or CAF. However, CAF was found to decrease activation in the precentral gyrus during the learning phase whereas both other drugs did not show any effect during encoding.

6.1 Memory task

6.1.1 Encoding

According to Tulving et al. (2002), encoding and recall are lateralized, whereas encoding is associated with left and recall with right hemispheric activity. Here, subjects also showed pronounced left hemispheric activity, whereas the activation pattern during recall is more ambiguous. Additionally, previous studies showed that verbal encoding is generally more pronounced in the left hemisphere than in its right counterpart (Frost et al., 1999; Szaflarski, Holland, Schmithorst & Byars, 2006).

Besides activations within the visual cortex, activations were detected in language processing areas as well as lateral frontal areas extending to the left DLPFC. Following the two-streams hypothesis (Goodale & Milner, 1992), object recognition is subdivided into the ventral and dorsal paths. Spatial object location is associated with areas extending from the visual cortex dorsal to parietal regions. During the learning task of this experiment, areas such as the inferior temporal lobe (ITL) as well as fusiform gyrus were activated. These regions could be accounted for the ventral “what” pathway that processes object identification. In line with a theory of hierarchical memory processing by Ranganath (2006), higher executive functions interact with visual object encoding. The activation of the left DLPFC and surrounding areas may act as a higher monitoring port that judges received words for order and significance. Furthermore, it was shown earlier that the DLPFC also provide strategies for a deeper encoding and hence support organization of memorized information (Fletcher et al., 1998). In this case here, the importance of temporal word order needs to be stressed. Subjects were aware that

single word memorization was not enough to meet the task requirements. The broad lateral PFC activation may account for cognitive control of the temporal order. For instance, patients with frontolateral brain damages showed no recognition or free recall deficits but significant problems to recall the correct temporal word order (Kesner, Hopkins & Fineman, 1994; Shimamura et al., 1990). The view that the DLPFC manipulate item memorization i.e. through entanglement, was also supported by imaging studies (review: Blumenfeld & Ranganath, 2007). Critically, this function is an additional feature that supports long-term encoding. The primary memory storage is not directly processed in the DLPFC but in the MTL (Simons & Spiers, 2003). However, in contrast to previous studies (i.e. Greve, Evans, Graham & Wilding, 2011), no specific hippocampal activation was detected here. Comparing successful and failed subsequent memorization, hippocampal activation tends to predict the successful recall of items, whereas ITL and fusiform gyrus generally process novelty of semantic content and word recognition, respectively (Kirchhoff, Wagner, Maril, & Stern, 2000; Nobre, Allison, & McCarthy, 1994). The encoding of single words was a premise, but not the main goal of this experiment. Subjects were instructed to memorize the temporal order of the presented words. In other words, they were required to reorganize the perceived information while encoding, and thereby, perform an additional, higher order memory process. This perfectly corresponds to a study on spatial navigation in which subjects had to navigate through a virtual environment either by first person or bird's eye view (Shelton & Gabrieli, 2002). Interestingly, subjects who navigated in their first person perspective, activated regions in the PFC as well as MTL. These results were not replicated by the bird's eye view group. Instead, they showed activation patterns within fusiform gyrus and ITL. The authors interpreted their findings in the way that the bird's eye group had to interlink information on their perspective with information about their environment. Interestingly, neither group showed any differences in accuracy despite their different neural footprints. Generally speaking, the integration of information into a major context was also part of our study. Here, single words had to be integrated into a temporal pattern. Taken these results and our data together, another neural encoding process besides MTL mediation can be assumed. It can be argued that the verbal memorization process of our study as well as the memory of more advanced navigation routes are both based on higher order memory processes. Taking the hierarchical nature of memorization into account, the activation of ITL and fusiform gyrus may reveal a higher order memory system. In conclusion, primary learning of words per se is not directly represented by the activated regions, but the memorization of the temporal

relation of different word clusters is processed by the above-mentioned regions. Moreover, in line with previous models, a top-down related mediation of prefrontal areas such as DLPFC on verbal encoding can be proposed from our data (Ranganath, 2006). According to this model, the primary encoded words are processed in specific verbal areas of the ventral path, namely ITL and fusiform gyrus, and temporally restructured by inputs of the DLPFC that was simultaneously activated during learning. How this process works in detail requires further research on verbal memory processing.

During the resting control condition, subjects showed activations that are usually assigned to the default mode network (DMN). Typically, regions around the PCC as well as medial PFC, parietal and temporo-insular areas were activated and functionally connected during resting but awake state of subjects (Greicius, Supekar, Menon, & Dougherty, 2009). Therefore, these specific activations cannot be interpreted as deactivations of learning specific processes but as the base of resting activity.

6.1.2 Recall

In contrast to the HERA assumption of right lateralized recall processing, our findings did not support a strict asymmetry in hemispheric activation pattern. While the role of frontal asymmetry is emphasized within the HERA model (Habib et al., 2003), emphasizing right frontal activity, this study revealed a more pronounced activation in the left frontal cortex. This contradiction is also seen in other reports and objects the generalization of the proposed asymmetry hypothesis; moreover it stresses the left hemispheric role of verbal retrieval (i.e. Wagner et al., 1998).

Besides left frontal activation, a significant area in the visual cortex and left ITL was activated. Taking the contrast and instruction for the control task into account (“don’t read, just count the syllables”), these activations correspond to brain areas that previously were identified as essential for reading single words (Fiez & Petersen, 1998).

In line with previous studies on temporal word order (Cabeza et al., 1997; Petrides, 1991), the frontal lobe as well as the dorsal parietal lobe seemed to play a significant role during memory recall. Since functional connections between dorso-frontal and parietal regions are assumed, these inferior parietal activations during the task may account for contextual information such as temporal planning (Cabeza et al., 2003; Kim, 2013). In the present case, the judgement of the right temporal order may have been processed through the left PFC and parietal brain areas and hence extend the dorsal

stream in temporal processing. A functional imaging study on healthy subjects showed that the magnitude of the parietal activation was related to the temporal distance between encoded items (Marshuetz, Reuter-Lorenz, Smith, Jonides, & Noll, 2006). Although we just took general temporal retrieval into account, the inferior parietal lobe could also have displayed temporal association between the retrieved words.

Furthermore, activation within bilateral caudate nucleus was detected. This region of the basal ganglia is associated with the processing of goal-directed behaviour and action-outcome contingency (Grahn, Parkinson & Owen, 2008). It seems crucial for subjects that feedback of their action is provided. However, this premise was not featured by our study design. Therefore, an alternative explanation for caudate activity derives from clinical populations. In non-medicated schizophrenic patients, caudate volume was associated with the prevention of error commitment and severity of symptoms (Levitt et al., 2002). The authors stressed a left lateralized association between volume decrease of the caudate and performance deficit in verbal working memory task. Together with our findings, especially the left caudate seems to take part in a broader network monitoring memory assessment. This view is supported by a recent encephalography (EEG) study that stressed the caudate function in guiding choices towards right or wrong categorization, with close links to the thalamus and pre-SMA (Hart et al., 2013). Taken together, the caudate may support the DLPFC and other higher monitoring centres in the correct retrieval of temporally categorized words.

During the control condition subjects' task was to count syllables of three different random words. Here, a broad activation pattern in several language-specific brain areas was revealed, namely occipito-temporal areas. Furthermore, this task also led to parietal activations. In contrast to the recall task, subjects showed more ventral parietal activations during the control task. In line with previous studies on language processing, the counting of syllables is likely to have caused this change in BOLD signal (Binder, Westbury, Mckiernan, Possing & Medler, 2005).

According to a theory on attention processing, within the parietal cortex there were different subregions identified that are responsible for specific distinct functions. While the dorsal parietal cortex mediates top-down guided monitoring, more ventral neurons conduct bottom-up driven attentional processes on external stimuli (Corbetta & Shulman, 2002). This theory is backed up by the data shown here. While top-down attentional processes determine the retrieval of learned temporal word order, bottom-

up stimuli detection supported the right choice of syllable lengths. Since attention and episodic memory share a similar region in the lateral parietal cortex, a close functional proximity can be assumed (review: Roberto Cabeza, Ciaramelli, & Moscovitch, 2012). However, other reports object to the idea of attentional recruitment during retrieval (Hutchinson, Uncapher & Wagner, 2009). Instead, the authors propose distinct neural regions that partly support each other, i.e. goal-directed attention processes on episodic retrieval, but dissolve mainly into the two distinct cognitive processes: attention and episodic memory. To further explore this dichotomy, a more detailed paradigm should be used in prospective studies.

6.2 Methylphenidate

6.2.1 Behavioral data

Consistent with previous studies, MPH did not alter direct performance, early free recall or speed of processing in the declarative memory task (Bray et al., 2004; Kuypers & Ramaekers, 2005; Linssen et al., 2012). However, in accordance with Linssen et al. (2012), MPH improved late free recall. Similar to our study, Linssen et al. (2012) tested a larger word list paradigm in order to avoid alleged ceiling effects when using list lengths that were too short. Subjects learned from a wordlist containing 30 items, which was subsequently repeated. The measure of performance was the number of correctly recalled words. Thirty minutes later they were asked again to recall as many items as possible. Furthermore participants in the study took part in a recognition test including two lists of 15 old and 15 new random words. Similar to our study, subjects on 20 mg and also 40 mg, but not 10 mg MPH, showed improved performance. Furthermore subjects displayed reduced response times in the recognition task after 40 mg MPH treatment. The difference between this previous and our present study is, that Linssen (2012) conducted the delayed recall after 30 minutes whereas our study used a 24 hour delay. Consistent with the view that neuroenhancement is meant to improve sustained encoding, our study as well as that of Linssen et al. (2012) failed to reveal any positive immediate recall effect. The authors proposed an enhanced consolidation process that is facilitated through MPH application. Whereas a larger attention span is often demonstrated in higher scores of immediate recall (Engle, 2002), the enhancement of delayed performance is potentially driven by another mechanism. Eventually, deeper encoding potential, in this case caused by MPH intake, led to longer lasting memory span. On a molecular level, it may be that MPH mediates long-term potentiation processes similar to those of amphetamines (Soetens, Casaer, D'Hooge & Hueting, 1995).

This is thought to translate content from short-term into long-term memory based on DA-dependent protein synthesis in the hippocampus (Lisman, Grace & Duzel, 2011).

Studies on the effects of emotional arousal and stress on memory processing demonstrated that arousal may lead to better information encoding (Christianson & Loftus, 1991; Revelle & Loftus, 1992; Eysenck, 1976). Likewise, external stress induction through epinephrine facilitated memory consolidation (Cahill & Alkire, 2003). MPH was shown to influence subjects' cardiovascular system and may thereby induce external arousal – similar to that produced by emotional stimuli. However, consistent with previous findings, no correlation between memory performance or delayed recall and increase in heart rate and blood pressure, respectively, could be observed (Del Campo et al., 2013; Mehta et al., 2000; Tomasi et al., 2011). Therefore, the mere increase in peripheral arousal is not sufficient to explain the observed performance improvement.

Since MPH studies investigating the effect on verbal memory are rare so far, it is worthwhile to take a look at other dopaminergic drugs and their effect on declarative memory (for review see Smith & Farah, 2011). Besides plenty of null effect reports, there are several studies showing a positive effect of d-AMP (i.e. Zeeuws, Deroost, & Soetens, 2010a, 2010b; Zeeuws & Soetens, 2007), L-Dopa (i.e. Linssen et al., 2014) and COMT-Inhibitors (Apud et al., 2007) on declarative memory performance. However, only d-AMP seemed to be effective in delayed recall (Soetens, D'Hooge, & Hueting, 1993; Zeeuws et al., 2010b; Zeeuws & Soetens, 2007) or delayed recognition (Zeeuws et al., 2010a), but not to be promising for immediate recall. Indeed, only Rapoport et al. (1980) demonstrated positive enhancement of d-AMP after a short delay recall. Smith & Farah (2011) stress the importance to focus on the design of studies that could not demonstrate positive memory effects of dopamine-modulating drugs. For tasks performed in the laboratory it is common to test memory function soon after acquisition. In doing so, there may be an underestimation of the extent of the effect of memory enhancement. Since most of the learning processes in the real world target enduring acquisition of memory, many studies investigating the drug effect of MPH/AMP do not picture realistic situations where people actually use NE.

Contrary to the hypothesis that low baseline performers benefit from NE to a greater extent, we could not find any support for this. In contrast to previous findings (Mehta et al., 2000), neither intelligence scores nor preliminary memory assessment determined later declarative memory performance benefit through drug use. However, subjects with high scores on ADHD assessment scales significantly benefited from MPH intake with regard to their late recall performance. In line with Del Campo et al., (2013), the baseline

of attention function predicted effectivity of DA amelioration. Independent of diagnosis, ADHD patients as well as healthy adults with low attention scores strongly improved their attention performance after MPH intake (Del Campo et al., 2013). Furthermore, it has long been suggested that attention and depth of processing of episodic information are closely linked with one another (Shallice et al., 1994). Connecting our results with those of Del Campo et al. (2013), MPH appears to improve memory performance in certain target groups, while subjects with a high degree of attention control do not show any improvements. It is incumbent on future research to identify more inter-individual differences that somehow interact with DA elevation.

Still, it is not clear how drug application is temporally linked to the effect on cognitive performance. Questions that still need to be answered are: When in time should we apply MPH to subjects in order to achieve the highest memory performance? Before or after encoding? Similar to other studies (Linssen et al., 2012; Rapoport et al., 1980; Zeeuws & Soetens, 2007), we administered MPH before the encoding task and hence, the whole memorization process including encoding, maintenance and recall was affected. However, it was suggested that stimulants operate after initial encoding processes and primarily facilitate memory consolidation (Zeeuws & Soetens, 2007). Another study using a different approach administered MPH 12 hours after encoding and therefore solely affected memory recall (Izquierdo et al., 2008). Subjects had to study facts contained in a brief text and recall their knowledge two and seven days later. If the application of MPH 12 hours post training still affected consolidation, further general questions with regard to the length of the labile consolidation period as well as the mediating effect of MPH arise and should be an object of research in the future.

Besides alterations in performance in delayed memory recall, subjects under MPH responded with higher confidence to the direct word order assessment without any advantage in direct word order judgement performance. This perception gap was also previously described in a meta-analysis (Repantis et al., 2010), where the authors found subjects to overestimate their performance when medication was applied. In line with this impression based on a survey among clinical surgeons, Franke et al. (2013) warned of risks through overestimation after NE consumption. Similarly, other authors cautioned against the subjective impression of improved performance without any effect in “the real world” (Advokat & Scheithauer, 2013).

An alternative explanation for subjects' confidence increase may be given through the general lift in subject's mood due to MPH. Since its similarities to amphetamines, i.e. increasing DA availability in the striatum (Volkow et al., 2001), MPH possibly increases mood and promote subjects to get a "high" (Sussman et al., 2006). According a theory on affection guidance (i.e. Clore & Palmer, 2009), different mood states may colour information processing. While positive affect reinforces already existing convictions, negative affect seems to promote critical evaluation and more stimulus-specific processing. The subjective well-feeling caused by MPH may have therefore promoted latent convictions of the task and have possibly lead to higher confident ratings.

6.2.2 Imaging data

Until today, no distinct pattern of MPH modulation on cognition could be observed (Table 1). Even in the same group of subjects, different cognitive requirements lead to different signal alterations under MPH (Clatworthy et al., 2009; Dodds et al., 2008). Furthermore, for different cognitive domains, distinct dose-effect relations of MPH were assumed. Contrary to earlier findings on working memory enhancement in animals and humans (Arnsten & Dudley, 2005; Cools & D'Esposito, 2011), declarative memory seems not to follow an inverted U-Shape relation; instead MPH improves memory in a linear fashion with dose elevation (Linssen et al., 2012). This study was performed with 20 mg MPH; further studies could concentrate on higher dosages in expectation of stronger effects as seen before. It remains to be seen whether dose and application type interact with performance in cognitive domains. Unlike most other imaging studies performed on the cognition effect of MPH before, we used a relatively low dose of MPH. However, our data showed a significant decrease in signal in several brain regions including the SMA, temporal, occipital and lingual gyri. These deactivations must not account straight for a lower performance grade. Instead it should be noted, that deactivations are well known in the literature as task-induced deactivations (TID) that may reflect a reallocation of neurocognitive resources and are modulated by the cognitive load of the demanding task (McKiernan, Kaufman, Kucera-Thompson & Binder, 2003). TIDs were previously linked to different cognitive qualities, including encoding processes (Daselaar, Prince & Cabeza, 2004) and working memory (Tomasi et al., 2011). While no difference was seen for encoding in this study, MPH affected the recall of verbal memory in subjects in comparison to placebo in the following regions.

Supplementary motor area

Situated medially of both hemispheres, anteriorly of the motor cortex (M1), the SMA is linked to movement initiation, sequence processing and conditioned behavioral learning. This area is connected to motor neurons and further projects to the DLPFC as well as basal ganglia areas. However, its distinct function remains unknown so far (Nachev, Kennard, & Husain, 2008). A recent PET study demonstrated a strong link between SMA and the DA system (Garraux, Peigneux, Carson, & Hallett, 2007). Additionally, pre-SMA and SMA were proposed to be involved in executive operations such as attention and learning from visual stimuli. Further, the authors of a review on attention processing came to the conclusion that neurons of the SMA are involved in timing processing and correct choice of sequential actions (Macar et al., 2002; Tanji, 2001). In the present experiment, subjects had to judge the correctness of a chronological sequence of words. Simultaneous reduction in SMA activity may reveal an increased efficacy in the correct retrieval of temporal order. Growing support for this claim comes from previous studies on MPH and amphetamines. It was suggested that reductions in cerebral blood flow accompanied by equivalent behavioral performance reflect an increased efficiency of task-related networks (Pauls et al., 2012, 2000; Mehta et al, 2000). Since catecholamines are known to modulate sensory processes in decreasing fashion (Foote, Freedman, & Oliver, 1975), the underlying mechanism of MPH may lie in the suppression of background noise and in turn an increased selection of environmental stimuli (Volkow et al., 2001). A similar argument was made by Tomasi et al. (2011) about their findings of deactivations within BA 23 and 31 during a working memory task. Their claim of a MPH-mediated increase in filtering may be also working for other DA sensitive areas such as the SMA and hence account for an increased task focus in subjects.

Superior temporal gyrus

Another significant cluster of deactivated voxels was found within the superior temporal gyrus during retrieval. Encompassing the primary auditory cortex, stimulation in the superior temporal lobe is widely known to be caused by auditory stimuli (Howard et al., 2000) as well as verbal hallucinations in schizophrenia patients (Allen et al., 2007). During a working memory task, psychotic patients showed activations in this region during task assessment, whereas the healthy controls revealed deactivations (Crossley et al., 2009). Hence, a relatively low activity within this brain area seems to be associated with optimal verbal working memory performance. Does a further reduction

in the superior temporal gyrus, i.e. through MPH application, increase memory performance?

On the other hand, it was reported that deactivations were accompanied by a lack of exploration behaviour (Gharabaghi, Fruhmann Berger, Tatagiba & Karnath, 2006). Nonetheless, a slight decrease may prove to be beneficial in reducing distractions through the decrease of exploration. A whole different explanation comes from a study that investigated temporal processing and identified the right superior temporal lobe as crucial for auditory temporal information (Bueti, van Dongen & Walsh, 2008). In contrast, in our study we used visual and verbal stimuli. It remains to be seen if future studies using different quality sets of stimuli can replicate activation in the superior temporal lobe with regard to temporal processing.

Inferior occipital gyrus & Lingual Gyrus

Both regions, the inferior gyrus and the lingual gyrus, are crucial in visual processing. Whereas the lingual gyrus seems to be responsible for global processing, the inferior occipital gyrus processes local information (Fink et al., 1996). Furthermore, the same authors reported a lateralization of visual attention in which the right hemisphere accounts for global and the left for local visual attention. The authors interpreted their results as evidence for very early top-down guided visual processing. The interaction of the recall task and MPH intake led to deactivations in the left lingual gyrus and inferior occipital gyrus. It can be speculated that MPH reduced attention on single words and led to the perception of the whole chunk containing three words in a row. However, since the deactivated clusters were relatively small, further studies need to investigate this question in more detail.

Together, these findings provide support for the hypothesis that MPH modulates episodic memory functioning by ameliorating certain brain regions. The increase in DA was shown to decrease selective parts of the brain that altogether increase the signal-to-noise ratio in attentional processes and thus eventually lead to better performance in delayed memory recall.

An alternative explanation approach may be summarized as increased efficiency hypothesis. Basically, efficiency is understood as a lower neural recruitment while no decline in behavioral performance is measured. Furthermore, the balance of activations and deactivations seems to be task-specific. With regard to working memory, signal deactivations were seen before and are thought to lead to a “maximization of resources

for the activated network“ (Tomasi, Ernst, Caparelli & Chang, 2006, pp. 694). For the recall task performed in the scanner, we could not see any difference in neither performance nor in reaction time while BOLD signal was reduced under MPH. As mentioned previously, the deactivated clusters may contribute to memory and language processing circuits. Thus it appears plausible that DA mediated innervation led to a decreased recruitment of neural activity within these regions. Support for this thesis comes from another study investigating the effect of MPH (Mehta et al., 2000). Besides fewer errors committed on a spatial working memory task, Mehta et al. (2000) could show an accompanying reduction in rCBF within the DLPFC in subjects. Similar, Apud et al. (2007) tested an n-back paradigm on healthy volunteers under the influence of Tolcapone, a COMT-inhibitor used in PD treatment. While the subjects' performance was similar to that under placebo, they showed decreased BOLD signal in the DLPFC. Akin to these findings, Mattay et al. (2003) showed that subjects with low prefrontal DA function benefit from d-AMP during a working memory task by increasing efficiency in the left PFC. Again here, a comparable level of performance under drug is set in the context of decreased BOLD signal in task-related brain areas. In summary, our results are entirely consistent with the above-mentioned neuroimaging studies, according to which MPH decreases regional CBF in certain brain regions presumably through the uplifting of endogenous DA innervation.

However, the investigation of the interaction contrast further showed that MPH acted in dependence on the cognitive process. The significance of the SMA cluster activity was caused not just because of a deactivation during recall, but also because of an increase of BOLD signal during the control condition (Figure 11). MPH therefore seems to activate voxels in the SMA area during lexical processing. The idea that SMA may be involved in speech production is not a new one. Surgical and electrophysiological studies have already reported on the importance of that region in speech production (Chauvel et al., 1996; Krainik et al., 2003). There is support for the hypothesis that motor regions, foremost the SMA, are also important in speech production and syllable selection (MacNeilage & Davis, 2001). The authors proposed a kind of frame modelling function of the SMA that is tightly linked to prefrontal areas such as BA 44 (Broca's area). There, the language content is supposed to be generated and connected with linguistic morphologic features of speech parts from the SMA. While our subjects were instructed to judge the syllable lengths of three presented words, they were asked not to process the semantic characteristics, but instead just to internalize the phonemic structure of

each word. To accomplish this task, one needs to at least read and eventually internally replicate the syllables. The processing of phonemic features was recently demonstrated in a fMRI experiment revealing BOLD signal activations in the SMA as well as left and right parts of the precentral gyrus (Alario, Chainay, Lehericy, & Cohen, 2006). To integrate our results into a coherent theory, two further findings need to be taken into account. First, language initiation and production is associated with endogenous DA release (Simonyan, Herscovitch, & Horwitz, 2013). And secondly, the SMA is a primary target for DA innervation (Gaspar, Stepniewska, & Kaas, 1992). Despite MPH's enhancing function in verbal learning, it appears plausible that MPH also facilitates word perception due to increasing activity in speech-associated areas. Since its distinct function remained ambiguous (see Figure 11C), MPH needs to be examined on the basis of distinct tasks to prevent this possible overlap of results in further studies.

6.3 Modafinil

6.3.1 Behavioral data

The data provided here are in line with the reports of a meta analysis (Repantis et al., 2010) that also could not reveal a positive memory effect of MOD in any sleep-deprived subjects. According to the authors of two working memory paradigms, subjects only improved their results after MOD in the high demanding task (Müller et al., 2013). Notably, subjects committed more errors during placebo compared to MOD, suggesting an increased arousal or attentional state induced by the drug. Further support for this hypothesis comes from Battleday & Brem (2015) who proposed MOD's enhancement ability in demanding challenges to the domains of executive functioning, attention and learning. This selective improvement is likely to be caused by MOD's interference with catecholamines of the frontal brain areas (Minzenberg & Carter, 2008). It seems that MOD elevates cognitive function in dependence on its dose (Turner et al., 2003). 200 mg compared to 100 mg improved reaction time during a stop-signal task, but left the other 10 tasks of a cognitive test battery unaffected. Furthermore, in our recall task, none of the subjects reached the maximum amount of correct responses. Moreover the spread of variance makes possible limiting ceiling effects unlikely in this case. It seems to be obvious that MOD does not necessarily improve declarative memory the way MPH affected memory enhancement. While previous studies could not find any improvements in delayed recall tasks, they point to a benefit of MOD in stimulus recognition (Müller et al., 2013; Randall et al., 2005). Since recognition of learned items was not part of our experiment, we may have missed a selective effect of MOD.

Altogether, our data as well as the literature suggested another scope of MOD effect in learning compared to MPH.

In contrast to Minzenberg, Yoon & Carter (2011), our data did not show any improvements in reaction time during MOD. While the subjects of our study had to focus on their performance in correct responses, the other study's main goal was the fast reaction. In line with others who investigated the neural effects of MOD on cognition in healthy adults (Ghahremani et al., 2011; Rasetti et al., 2010; Schmaal et al., 2014), behavioral alterations such as variations in reaction time must not necessarily be affected by MOD application. Attention processes such as the anticipation to rapidly react towards a stimulus onset is highly dependent on frontal brain resources (Stuss et al., 2005) as well as optimal catecholamine equilibrium (Arnsten & Li, 2005). Since MOD has just a moderate influence on DAT and NAT compared to amphetamine-like drugs (Minzenberg & Carter, 2008), it eventually was too low in this case to increase reaction speed.

The assessment of vital signs did not show any increase over the time course after MOD administration. The reviewed studies on MOD's effect on cognition (Table 2) that used the same single dose of 200 mg did not report any side effects either (i.e. Minzenberg et al., 2011; Schmaal et al., 2013) or did not mention any physiological data at all (i.e. Funayama et al., 2014; Goudriaan et al., 2013). Ellis et al. (1999) and Volkow et al. (2009) on the other hand, administered 400 mg MOD to their subjects. Ellis et al. (1999) did not observe any significant increases in vital signs, but mentioned side effects such as dryness of the mouth and headache. Furthermore, Volkow et al. (2009) reported significant increases of blood pressure and heart rate. In an experiment on drug effects on energy uptake reduction and circulation mediation, Makris et al. (2004) reported the cardiovascular impact of different oral MOD doses. Only the highest dose group (7.0 mg/kg) which corresponds to 560 mg in a person weighing 80 kg, showed an increase of up to 10% in heart rate and blood pressure. The moderate group (3.5 mg/ kg body weight), which corresponds to 280 mg in a person weighing 80 kg, just showed minimal cardiovascular increases. In conclusion, the MOD dose that is used in clinical settings as well as in the present study seems to be too low to show any cardiovascular side effects.

6.3.2 Imaging data

Unlike previous studies on the enhancing effect of MOD on working memory (Minzenberg et al., 2008; Rasetti et al., 2010), we could not identify any task-related

manipulation on the neuronal level. However, only when taking MOD, bilateral DLPFC activations as well as inferior temporal and parietal region activations reached significance during recall. These regions were more strongly activated on the left side and may be responsible for a beneficial effect of MOD in verbal processing. In general, these regions correspond to the activated regions during recall across all subjects. Interestingly, this task-dependent contrast did not show similar activations under placebo. This, plus the finding that no significant drug-task-interaction could be revealed, suggests that MOD slightly increases the distinction between different cognitive demands such as recall and verbal processing. The lack of any main drug effect as well as interaction effect is also reflected in the no effect results of other studies (Schmaal et al., 2013; Schmaal et al., 2014). Taken together, it seems that MOD augments brain activation for certain tasks demanding executive functioning such as task switching (Minzenberg et al., 2008) and working memory (Rasetti et al., 2010). On the other hand, memory recall seems to be a complex process that is facilitated through different brain regions (Figure 9) and is perhaps not prone to MOD modulation.

6.4 Caffeine

6.4.3 Behavioral data

Besides CAF's supposed enhancing properties on sleep-deprived individuals (Kilpeläinen, Huttunen, Lohi & Lyytinen, 2010) and moderate beneficial effects in attention and psychomotor performance in healthy non-sleep-deprived-subjects, the data on memory enhancement is not clear (for review: Nehlig, 2010). Our data suggested that CAF does not alter memory performance in direct retrieval or in free early recall. Generally, this view is supported in the literature. For short-term memory, most studies do not report any drug effect i.e. early recall and retrieval. Of 25 reviewed studies on a beneficial memory effect of CAF, 6 found a positive effect, 3 revealed negative memory impact and 16 could not find any difference to placebo at all (Nehlig, 2010). Likewise, CAF did not lead to an increase in free recalled items during free late recall after 24 hours. Compared to short-term memory assessment, not many studies are available on this subject so far. For instance, Herz (1999) conducted an experiment with 48 CAF-naïve subjects who were instructed to learn 16 items of a words list. 48 hours later they were asked to recall as many words from the memorized list as possible. Similar to our study, a subgroup of 12 subjects received CAF during encoding but not during retrieval. No difference could be observed compared to another group that received placebo. In contrast to our study, subjects received a 5 mg/ kg body weight

dose CAF which was nearly double our dosage. Since CAF is thought to follow an inverted U-Curve with regard to arousal (Nehlig, 2010), our results and the ones by Herz (1999) are hardly comparable due to a different position on the U-Curve. Another study investigated the distinct CAF effect in middle aged (45-60 years) vs. older adults (60-75 years) also failed to reveal any difference between drug and placebo in delayed recall (Schmitt, Hogervorst, Vuurman, Jolles, & Riedel, 2003). The authors administered 100 mg to each subject, which corresponds to half of our dose. These two studies and our own results together, covered a large range of dosages and none of the studies could reveal any effect. Although the impact of three single studies with entirely different designs is limited, one could suggest, that CAF's ability to enhance memory is low or non-existent.

Interestingly, CAF worsened reaction times in correct task responses. This is remarkable because usually CAF application was associated with a decrease in reaction times in various tasks such as simple selective discrimination (Lorist, Snel, Kok, & Mulder, 1996) or simple reaction tasks (review: Smith, 2002). The positive CAF mediation is likely to be dependent on habitual usage, thus improvements in reaction times are more distinct in heavy consumers (Smit & Rogers, 2000). This phenomenon known as withdrawal-relief hypothesis (Rogers & Dernoncourt, 1998) cannot be taken into account due to the fact that in our subjects self-reports' about their drug consumption, they denied the use of coffee consumption. Furthermore, the relief of CAF abstinence is associated solely with an increase in performance and decrease in reaction times. Then, how can slower response behaviour be linked to CAF consumption? In fact, CAF inconsistently improves performance and reaction times: While advantages are seen for simple tasks, it is likely that more complex cognitive demands are not affected or even impaired by CAF administration (Nehlig, 2010). Perhaps the lack of enhanced performance and deterioration in reaction times in the temporal judgement task was caused by its excessively high cognitive demands.

6.4.2 Imaging data

While the recall task did not induce any signal alterations, subjects exhibited bilateral precentral gyrus deactivations as well as BOLD alterations in the left parietal operculum during the encoding phase.

Precentral gyrus

A cluster of 50 deactivated voxels within the bilateral precentral gyrus was identified during for the interaction Encoding X CAF. This distinct anatomic region with a high density of Betz cells reflects the human primary motor cortex. Within this region, the somatotopic representations of body muscles are mapped into a cytoarchitectonic arrangement called motor homunculus. Despite some variance in those maps, the identified cluster corresponds to an area that usually reflects movements of the feet (Meier, Aflalo, Kastner, & Graziano, 2008). In addition, recent findings in the literature linked the motor cortex 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). However, a deactivation in the medial precentral gyrus that corresponds to certain cognitive phenomena was not 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 recall. On the other hand, the simultaneous deactivation of medial and lateral parts of the precentral gyrus may have facilitated the act of reading of the presented words. Perhaps, less neurons were recruited while subjects were reading under the influence of CAF. Our data is not definite enough yet to make a further assumption about the effect of CAF on the medial precentral gyrus while learning.

Parietal operculum

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. The parietal operculum is a secondary somatosensory cortex (SII) that can be subdivided into 4 cytoarchitectonic subregions and spans functional connections to other related sensory areas (Eickhoff et al., 2010). Anatomical and functional connections from the parietal operculum extend to pre- and postcentral gyri as well as to the frontal cortex. Besides its proposed main function of sensory-motor integration (i.e. Wasaka et al., 2005), authors of another study reported functional importance of the operculum for sensory sequence learning (Romo, Hernández, Zainos, Lemus, & Brody, 2002). Besides motor tasks, the operculum seems to be responsible for general verbal processing (Wagner et al., 1998b). Similar to our data, Abel et al. (2012) found deactivations within

the parietal operculum when subjects performed a lexical task (Abel, Dressel, Weiller, & Huber, 2012). There, subjects had to name target pictures while being distracted by phonological words that were either related or unrelated to the target category. For category matching distractors, among several other sensory processing regions, the operculum was suppressed. In contrast, in our study subjects had to encode verbal stimuli that were later recalled whereas Abel et al. (2012) examined the effects of priming and distraction. Deactivations in sensory areas during lexical priming were proposed to be responsible for an increase in efficiency (Abel et al., 2012). Eventually this also holds for learning processes. This deactivation might reduce cognitive distractions during verbal encoding. The focus on the semantic structure and hence perhaps on the temporal word order may got enhanced through the CAF-dependent decrease.

Anyhow, this region is not part of classic memory-related brain regions and other explanations for the deactivated cluster are possible. Moreover, it is likely that the other contrast, in this case the resting vs. learning, was responsible for the detected activity. Subjects were holding a button-box in their right hand to perform the subsequent recall task. The operculum receives input from S1 that, in turn, processes tactile stimuli of the contralateral hemisphere (Eickhoff et al., 2010). Furthermore, Young and colleagues reported that healthy adults exhibit increased BOLD signal within the parietal operculum during an attentional task on tactile discrimination (Young et al., 2004). Although we did not check for thoughts retrospectively, one can assume that subjects focus their attention on the button-box in their hand while being at rest. This device was the only tactile stimulus during the scan period and may therefore have activated primary and secondary motor regions.

Taking into account that CAF is a non-selective adenosine antagonist, CAF binds to a similar degree to A_1 und A_2 receptors (Koppelstaetter et al., 2010). While cardiovascular activity is predominantly associated with A_2 receptors, neural modulation is rather transmitted via A_1 receptors (Laurienti et al., 2003). The expression of A_2 receptors on the neocortex is rather low compared to basal ganglia and olfactory tubercle (Moreau & Huber, 1999). From that perspective, reductions in regional CBF are not likely to be the cause of BOLD signal of the interaction contrast. Hence, it can be assumed that CAF indeed causes neural modulating effects on motor and sensory regions.

Nonetheless, both CAF-induced processes, alterations in central blood vessels as well as neural activity, are thought to interfere with the BOLD signal (Bendlin et al., 2007). The CAF induced reduction of baseline CBF led to the hypothesis that CAF may be used as BOLD contrast enhancer (Mulderink et al., 2002). The idea was that CAF lowers the baseline BOLD signal, i.e. through reduction of global CBF during resting state, and increases the range of signal when cognitive load is upregulated, i.e. through regional CBF increase.

This idea was rejected by Laurienti and colleagues (2003). Likewise, they showed that subjects' CBF was reduced after taking CAF. However, they could not intensify the BOLD extent after sensory stimulation. Moreover, one subpopulation increased, whereas the other decreased BOLD signal after taking CAF (Laurienti et al., 2003). They concluded that there was a complex interplay of CAF, neural and vascular effects and individual adenosine receptor formations in subjects. The extent of receptor affinity and expression varies according to the dose, the duration and the frequency of ligand occurrence (Bespalov, Müller, Relo, & Hudzik, 2016). Therefore, the question of consumption habits may play a crucial role for interpreting BOLD signal alterations (Laurienti et al., 2002). However, this study was pre-screened for non-coffee consumers. Noise deriving from withdrawal relief (Rogers & Dernoncourt, 1998) and variations in coffee consumption within subject population (Laurienti et al., 2002) can therefore be dismissed. Still, the overall amount of caffeinated intake should be more carefully assessed in future studies.

CAF's effect on brain function was object of research in numerous previous studies (see Table 3). However, most of the investigated functional imaging studies either examined CAF function in resting state (i.e. Wu et al., 2014) or its effect in sensory perception (i.e. 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 young (Klaassen et al., 2013; Koppelstaetter et al., 2008) and older subjects (Haller et al., 2013; Haller et al., 2014). Compared to these working memory studies, we did not detect any activity enhancement in prefrontal or cingulate areas. Koppelstaetter et al. (2008) let subjects perform an n-back task while on CAF or placebo. Though applying half the dose of our design, the task-drug interaction in their study revealed activations in the medial frontopolar cortex (BA 10) as well as parts of the anterior cingulate cortex (BA 32). Those areas are usually associated with planning and reasoning (Braver & Bongiolatti, 2002), but not necessarily with encoding, which was

the main focus in our study. In Klaassen et al. (2013) subjects under the influence of CAF or placebo were assessing a Sternberg task within the scanner. Similar to Koppelstaetter et al. (2008), the drug-task-interaction pointed towards an increased signal within the PFC during encoding. Furthermore they could show activations in the left thalamus during maintenance. In contrast again to our study, subject received just 100 mg CAF. Considering the positive results of both studies together, the 200 mg dose of our study may eventually exceed an optimum that is needed for drug-dependent cognitive enhancement (Kaplan et al., 1997). Despite different results during encoding, our no-effect results regarding the recall condition are in line with those of Klaassen et al. (2013), who also reported negative findings there. Both studies examining CAF effects in older subjects (Haller et al., 2013; Haller et al., 2014) reported highest activations within striatal areas for the interaction CAF X n-back task. However, Moreau & Huber (1999) showed that especially within the basal ganglia, the highest amount of A_2 receptors are found. Therefore, the above-mentioned results from Haller et al. (2013, 2014) regarding working memory substrate should be handled with care. In this case, a predominant vascular effect seems to be more plausible than neuronal activity enhancement. Furthermore, their findings are based on an old subject population and are not necessarily applicable to young subjects (Sander, Lindenberger, & Werkle-Bergner, 2012).

Although encoding produced signal alterations within precentral gyrus and left operculum, no behavioral correspondence could be identified. The proposed discrepancy between cognition and behaviour on the one side, and brain imaging on the other, is a common finding in pharmacological research (i. e. Müller et al., 2005; Rasetti et al., 2010). In fact, imaging describes a phenomenon without claiming to identify the cause of the observed behavioral alterations. The apparent behavioral representation of a latent cognitive process is an integration of several brain processes. Here, fMRI is one way to map the link between behaviour and brain function (Wilkinson & Halligan, 2004). Similar to other stimulants that act on physiological parameters, central vascular as well as somatic effects may further interact with behaviour although we could not determine it with fMRI.

6.5 Study limitations

Several limitations of this study need to be acknowledged and addressed in the future. First, we did not control for drug plasma level to estimate the definite amount of

centrally acting active drug agent. Instead, we related drug amount to body weight, however by doing this, we missed individual pharmacokinetics. Furthermore, we did not set up a prior drug-effect-profile for each subject. For instance, MPH is poorly metabolized in subjects exhibiting a certain gene polymorphism (Linssen et al., 2012). Furthermore, baseline DA has been shown to influence the effect of DA alterations and should potentially be controlled for (Volkow et al., 2002). A quick and easy way to assess DA plasma concentration would be to record of changes in prolactin levels as a surrogate marker for DA concentration. It shows a negative relation to DA concentration and could be used to identify DA peak changes (Ben-Jonathan & Hnasko, 2001).

Second, our subjects participated twice during the same time of the day. However, we did not control for food-drug-interaction, even though there might be some interaction risk between the tested drugs and food ingredients (Midha et al., 2001).

Third, not only CAF, but all drugs in general give rise to the question of whether pharmacological fMRI is the best method of detecting drug effects. At least CAF seems to interact with cardiovascular responses independently of neural effects. Hence, a combination of BOLD and other methods should be considered. For instance, CBF alterations may be controlled with arterial spin labeling and cortical brain activation with EEG (i.e. Diukova et al., 2012). Furthermore, MPH has been shown to affect vital signs already in clinical dosages. Therefore, general arousal and body perception should play a more prominent role in future studies.

Fourth, the size of each drug group was quite small. Even though functional MRI studies usually deal with small numbers of subjects (see Tables 1-3), one may run the risk to overlook weak drug effects of clinical relevance. Furthermore, we included a certain number of students with many years of education. Although particular students are thought to use NE, we possibly biased our results using subjects with too high performance baselines.

6.6 Conclusions

Our study has important implications for the understanding of neuroenhancement and the question why certain drugs are used by people to support their learning and working abilities. While we report distinct effects for CAF and MPH with regard to performance measures as well as deactivations in specific brain areas, no obvious effect could be seen for MOD in non-sleep deprived subjects. Our findings indicate that single dose application of MPH improves memory performance, particularly in late free recall.

Furthermore, it seems to lift participants' subjective confidence of their own judgements whereas no direct corresponding performance effect could be detected. During the direct memory assessment MPH subjects showed deactivated signal within several brain regions that may reflect an increase in efficacy in data processing. Alternatively, our data may show that MPH emphasizes the processing of speech in language-related brain areas.

Furthermore, our data may allow insights into learning related processes in a healthy population. Our results may contribute to a deeper understanding of learning disorders that accompany various DA-sensitive cognitive disorders, such as ADHD (Del Campo et al., 2013), PD (Dauer & Przedborski, 2003) and schizophrenia (Howes & Kapur, 2009).

Further studies are needed to clarify the effect of performance-enhancing drugs and thus bring the emotional debate of NE on a more objective level.

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8. Attachment

Word lists of the memory task

Session 1:

Note, Pyramide, Geweih, Zebra, Zeitschrift, Teig, Elefant, Griff, Vorhang, Lachs, Spinne, Zimmer, Popcorn, Sänger, Schrott, Tinte, Karte, Hemd, U-Bahn, Frau, Socken, Geschirr, Auto, Rauch, Bienenstock, Holz, Roller, Späne, Lineal, Bach, Lama, Familie, Kanne, Wasser, Schlaf, Vogel, Landschaft, Drache, Farbe, Hirsch, Bohne, Boden, Apfel, Steckdose, Bett, Handtasche, Eis, Wirbel, Kellner, Tastatur, Gold, Beleg, Schiedsrichter, Weg, Zaun, Weste, Sekretärin, Knopf, Schachtel, Papier, Marine, Ball, Palast, Industrie, Geld, Patient, Kirmes, Wetter, Schach, Teller, Lkw, Netz

Session 2:

Fax, Wolle, Bühne, Regal, Zitrone, Hund, Traktor, Musik, Stuhl, Deckel, Kilometer, Wanze, Retter, Lehrerin, Tür, Storch, Bluse, Küste, Diamant, Blut, Porto, Gabel, Himmel, Kuh, Museum, Stadt, Flasche, Tiger, Limonade, Tulpe, Eisenbahn, Meer, Ritter, Diskette, Ring, Abfall, Stall, Dose, Krankenschwester, Sammlung, Klebstoff, Küche, Gemälde, Brief, Schlange, Bronze, Mann, Knöchel, Hopfen, Kaffee, Schmied, Wanne, Wohnung, Maus, Schnecke, Garten, Biss, Kiste, Statue, Schloss, Fahne, Radio, Nacht, Gruppe, Brot, Reifen, Zollstock, Dudelsack, Fluss, Dieb, Lappen, Nase

Eidesstattliche Versicherung

„Ich, Lucas Adam, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Functional Imaging in Neuroenhancement selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

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11.01.2017

CURRICULUM VITAE

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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