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Title: Neural effects of methylphenidate and nicotine during smooth pursuit eye movements

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Abstract

Introduction: Nicotine and methylphenidate are putative cognitive enhancers in healthy and patient populations. Although they stimulate different neurotransmitter systems, they have been shown to enhance performance on overlapping measures of attention. So far, there has been no direct comparison of the effects of these two stimulants on behavioural performance or brain function in healthy humans. Here, we directly compare the two compounds using a well-established oculomotor biomarker in order to explore common and distinct behavioural and neural effects. *Methods:* Eighty-two healthy male non-smokers performed a smooth pursuit eye movement task while lying in an fMRI scanner. In a between-subjects, double-blind design, subjects either received placebo (placebo patch and capsule), nicotine (7mg nicotine patch and placebo capsule), or methylphenidate (placebo patch and 40mg methylphenidate capsule). *Results:* There were no significant drug effects on behavioural measures. At the neural level, methylphenidate elicited higher activation in left frontal eye field compared to nicotine. *Discussion:* While increased hemodynamic response under methylphenidate is interpretable as enhanced processing of task-relevant networks, the reduced activation of task-related regions under nicotine could be associated with more efficient neural processing. Together, these findings suggest dissociable neural effects of these putative cognitive enhancers.

Keywords: cognitive enhancer, nicotine, methylphenidate, eye movement, smooth pursuit, fMRI

1. Introduction

Pharmacological compounds targeting neuromodulatory transmitter systems to enhance cognitive function in healthy individuals have been receiving considerable interest (Husain and Mehta, 2011; Maier et al., 2015; Ragan et al., 2013). Nicotine and methylphenidate are two widely used compounds that qualify as putative cognitive enhancers due to evidence of beneficial effects in both patient and healthy populations across different cognitive tasks (Lanni et al., 2008). Previous literature confirms overlapping effects of these compounds on different attentional tasks in humans (Koelega, 1993), but also differential effects on attention measures in rodents (Bizarro et al., 2004). So far there has been no direct comparison of these two stimulating agents in healthy humans.

Nicotine effects are mediated through nicotinic acetylcholine receptors located across the cortex (Wallace and Porter, 2011). Whilst there is consistent evidence of nicotinic enhancement of attention in animal models (Hahn et al., 2003) and neuropsychiatric disorders such as attention-deficit hyperactivity disorder (ADHD), schizophrenia and Parkinson's disease (Kelton et al., 2000; Petrovsky et al., 2013; Poltavski and Petros, 2006), in healthy individuals the enhancing effects on cognitive performance are less pronounced, but confirm positive effects on alertness and attention (Heishman et al., 2010; Sacco et al., 2004).

Likewise, enhancing effects on cognition are observed with the indirect dopaminergic agonist methylphenidate, the first-choice treatment for children and adults with ADHD (Agay et al., 2014). Major binding sites include striatal (Volkow et al., 1994) and extrastriatal dopamine transporters (Montgomery et al., 2007), but also noradrenalin transporters (Hannestad et al.,

2010). In healthy subjects improvements of cognitive performance under methylphenidate are ascribed to the stimulant-induced increase in attention and vigilance (Linssen et al., 2014).

The use of oculomotor tasks offers an advantageous tool to evaluate pharmacological effects on cognitive and motor functions (Reilly et al., 2008). The smooth pursuit eye movement (SPEM) task requires a mechanism to track a moving object in extra-personal space without head movement and draws upon attention, motion processing and temporo-spatial prediction (Barnes, 2008). The neural correlates of the required sensorimotor feedback system are well established in both humans and non-human primates and include motion processing regions, such as area V5, and attention and prediction-related regions in frontal and parietal cortices, namely frontal, parietal and supplementary eye fields and subcortical structures such as thalamus and putamen (Lencer and Trillenberg, 2008; Meyhöfer et al., 2015; Thier and Ilg, 2005).

Improvement of smooth pursuit performance with nicotine administration has been observed in saccade rate and maintenance gain (Dépatie et al., 2002; Domino et al., 1997; Klein and Andresen, 1991; Olincy et al., 1998; Sherr et al., 2002), but some studies also report deterioration of performance (Sibony et al., 1988; Thaker et al., 1991).

Neuroimaging studies in patients with schizophrenia and healthy controls have shown that nicotine reduces activity in the anterior cingulate gyrus in controls, but not in patients, during a SPEM task with constant velocity (Tanabe et al., 2006). Furthermore, in schizophrenia patients there was less activity in right hippocampal regions and bilateral parietal eye fields but improved performance under nicotine compared to placebo (Tregellas et al., 2005).

Smooth pursuit eye movements are not significantly impaired in children with ADHD which suggests that fronto-striatal abnormalities driving ADHD symptoms might not affect smooth

pursuit pathologically (Karatekin, 2007; Rommelse et al., 2008). Yet, methylphenidate which amplifies dopaminergic and noradrenergic signalling in fronto-striatal regions has been shown to improve pursuit performance in children with ADHD and healthy adults (Allman et al., 2012; Bylsma and Pivik, 1989). There are no imaging studies of methylphenidate effects on smooth pursuit; however, previous literature suggests that the localization of methylphenidate effects may be task-dependent (Costa et al., 2013; Dodds et al., 2008; Pauls et al., 2012) and modulated by the effects of the compound on dorsal attention and default mode networks (Liddle et al., 2011; Linssen et al., 2014; Marquand et al., 2011; Mueller et al., 2014; Tomasi et al., 2011).

Both nicotine and methylphenidate have been found to improve pursuit maintenance gain (Allman et al., 2012; Dépatie et al., 2002), although they primarily act on different neurotransmitter systems. So far, however, there are no direct comparisons of nicotine and methylphenidate that explore shared and distinct characteristics of their enhancing effects in healthy subjects. The recent ethical debate on pharmaceutical cognitive enhancement (Fond et al., 2015; Maier et al., 2015; Whetstine, 2015) and the high variability in treatment effectiveness of dopamine targeting compounds in patients (Cools, 2006; Jasinska et al., 2014; Kelton et al., 2000; Kieling et al., 2010; Martinez et al., 2011) demand a clearer picture of the substances' effects on neuronal processes and cognition. To better understand the common and distinct mechanisms of action, the current study assessed the effects of single doses of nicotine and methylphenidate on smooth pursuit eye movements, a perceptual-motor task previously shown to be influenced by these two compounds. We investigated the effects of acute nicotine and methylphenidate on blood-oxygen-level-dependent (BOLD) signal and recorded eye movements of healthy male non-smokers during smooth pursuit of a sinusoidal target. We hypothesised that both compounds

improve smooth pursuit performance, though the investigation of the neural correlates of improvement is exploratory.

2. Methods and Materials

2.1 Subjects

The study was approved by the ethics committee of the Department of Psychology at the University of Bonn. Subjects were recruited via advertisements posted on university boards and screened via telephone interview for a first set of inclusion and exclusion criteria. Inclusion criteria were healthy right-handed male non-smokers, free of current physical illness as well as no history of psychiatric disorders. Exclusion criteria were eye-sight or eye movement deficits, lifetime consumption of more than seven cigarettes, any current prescription or over-the-counter medication, any personal history of head injuries with loss of consciousness, any current Axis I diagnosis and any current or history of psychotic disorders (as assessed with the MINI International Neuropsychiatric Interview; Ackenheil *et al*, 1999), claustrophobia, body shrapnel or other metals, pacemakers and implanted prosthesis. After telephone screening potential candidates attended a medical examination at the University Hospital Bonn. The medical examination served to detect further exclusion criteria, such as poor physical health, signs of neurological impairments. Only after the physician's approval, subjects were invited to take part in the imaging procedure. All subjects provided written, informed consent and were compensated for their time and travel.

2.2 Design and Procedure

A between-subjects, placebo-controlled, double-blind design was applied. Subjects were randomly assigned to one of three treatment groups: 40mg methylphenidate, 7mg nicotine, or placebo.

The administered dosage of 40mg oral methylphenidate has previously been shown to affect BOLD during different cognitive tasks (Costa et al., 2013; Farr et al., 2014; Pauls et al., 2012; Ramaekers et al., 2013; Sripada et al., 2013). The dose is comparable to a therapeutic daily dosage for an adult with ADHD and is expected to block approximately 72% of dopamine transporters (Volkow et al., 1998). Previous studies have shown that oral dosage of methylphenidate achieves peak plasma level after about 60 minutes (Swanson and Volkow, 2002; Volkow, 1995; Volkow et al., 2001), therefore subjects were scanned one hour after capsule administration. The identical looking placebo capsule contained lactose.

A 7mg transdermal nicotine patch (NiQuitin Clear 7mg, GlaxoSmithKline, Germany) was applied to the upper back by a research assistant who was not involved in the scanning procedure. This method has led to reliable effects on eye movements in previous studies (Petrovsky et al., 2012; Schmechtig et al., 2013), with nicotine reaching peak plasma level three hours after application (a nicotine plateau level is achieved after 2 to 4 h after application according to the Summary of Product Characteristics of NiQuitin Clear). The placebo patch contained capsaicin to elicit itchiness similar to the nicotine patch (Rheumaplast, 4.8mg, Hansaplast, Germany). Placebo patches were cut to the approximate size of the nicotine patches (3x2cm).

Subjects were asked to abstain from alcohol the day before the scanning appointment and to arrive at the facilities well rested. On the day of assessment, subjects were administered the

Edinburgh Handedness Inventory (Oldfield, 1971) and a measure of verbal intelligence (Mehrfachwahl-Wortschatz-Intelligenztest, Version B, MWT-B; Lehrl, 1995; maximum score: 37). Each subject received a patch and two hours later a capsule. They were administered (a) a nicotine patch and a placebo capsule, (b) a placebo patch and a methylphenidate capsule or (c) a placebo patch and a placebo capsule. One hour after capsule administration, the imaging procedure started. During the waiting period, subjects remained in the MRI facilities and stayed abstinent from food and beverages except water.

2.3 Stimulus Presentation and Eye-Movement Recordings

Subjects lay supine on the scanner bed and viewed a 32-inch MRI compatible TFT LCD monitor (NordicNeuroLab, Bergen, Norway; resolution: 1024x768 pixel, refresh rate: 120Hz) standing at the rear end of the magnet bore via a first-surface reflection mirror mounted on the head coil. The distance from the eye to the monitor was approximately 172cm. An MRI compatible video-based combined pupil corneal reflection tracker (EyeLink 1000, SR Research Ltd, Canada) was situated at the bottom of the monitor and recorded movements of the right eye. The signal sampling rate was 1000Hz. A horizontal three-point calibration spanning the maximal horizontal range of target movement was applied prior to fMRI data acquisition.

Oculomotor data were analysed using DataViewer software (Version 1.11.900, SR Research Ltd, Canada) and task-specific graphical user interface based on LabVIEW (National Instruments Corporation, USA).

2.4 Smooth Pursuit Eye Movement (SPEM) Task and Analysis

The SPEM paradigm was identical to the task used in Meyhöfer *et al* (2015). In brief, the task was presented in a block design consisting of ten pursuit blocks and nine fixation blocks. The

target was a white circle (width and height 15 pixels, no filling, stroke width 5 pixels) on a black background. During fixation blocks the target remained in the centre position (0°). In the pursuit blocks the target moved horizontally in a sinusoidal waveform starting in the centre position and subtending a visual angle of ±5.8°. Frequency was either 0.2Hz or 0.4Hz, with each being used in five blocks. Each block lasted 30s and fixation blocks always followed pursuit blocks. The order of blocks was the same for all subjects (0.2Hz/FIX/0.4Hz/FIX /0.4Hz/FIX/0.2Hz /FIX/0.4Hz/FIX/0.2Hz/FIX/0.4Hz/FIX/0.4Hz/FIX/0.2Hz/FIX/0.2Hz). Prior to scanning, subjects received written instruction to follow the target with their eyes as accurately as possible and fixate on the stationary target during fixation blocks.

2.5 Image Acquisition

Imaging data were acquired via a 3T Siemens Trio Scanner (Siemens, Erlangen, Germany) at the Life & Brain Centre, Bonn. Subjects wore earplugs and foam padding was used to reduce head motion. During the smooth pursuit task 239 functional images of the brain depicting the blood-oxygen-level-dependent (BOLD) response were obtained using a T2*-weighted gradient-echo planar image (EPI) sequence (TR=2500ms; TE=30ms; flip angle=90°). Each image volume consisted of 37 slices obtained sequentially in descending order, each 3mm thick with an interslice gap of 0.3mm and an in-plane resolution of 2x2mm^2 (FOV=192×192mm^2, matrix=96×96). A standard twelve-channel head coil was used for radio reception and transmission. Slices were oriented to the intercommissural plane (AC-PC line). Subsequently, a high-resolution structural image was acquired using 3D MRI sequences for anatomical co-registration and normalization (TR=1660ms, TE=2.54ms, flip angle=9°, matrix=320×320, FOV=256×256mm^2, slice thickness=0.8mm).

2.6 Statistical Analyses

2.6.1 Behavioural Data

The first and the last half-ramp in each pursuit block were excluded which resulted in 180 complete ramps for behavioural analysis: 60 ramps in the 0.2Hz and 120 ramps in the 0.4Hz frequency condition. Subjects with high signal drop-out (less than 11 ramps in each frequency condition) were excluded from all further analyses. Saccade, gain and root mean square error (RMSE) scores were calculated separately for each frequency condition.

Saccade frequencies (N/s) were computed using minimum amplitude 1° and frequency (30°/s) criteria for the detection of saccades. Time-weighted average maintenance gain was calculated for sections of pursuit in the average 50% of each ramp by dividing mean eye frequency by mean target frequency for sections without saccades and blinks. Mean RMSE scores were computed for all included ramps, excluding blinks but including saccades.

A 2x3 mixed design analysis of variance (ANOVA) was applied with Frequency (0.2Hz and 0.4Hz) as within-subjects factor and Group (methylphenidate, nicotine and placebo) as between-subjects factor. SPEM variables were screened for violation of normality of distribution. For *post-hoc* comparisons, the p-threshold was adjusted for multiple comparisons with Holm-Bonferroni correction (Holm, 1979). All statistical analyses of oculomotor data were implemented in SPSS Release 22 (IBM Corp, USA).

2.6.2 fMRI Data

Image processing was conducted using Statistical Parametric Mapping software (SPM8; Wellcome Department of Imaging Neuroscience, UK) running in Matlab 2014a (Mathworks,

USA). To facilitate coregistration, all images were first manually reoriented by setting the origin to the anterior commissure. Functional images were realigned to the first image in the time series to correct for inter-scan motion and co-registered to the individual anatomical image. Transformation parameters from the segmented anatomical image were used for normalisation to standard stereotaxic space (Montreal Neurological Institute, MNI). Noise was reduced by smoothing functional images with an 8-mm full-width at half-maximum (FWHM) Gaussian kernel.

To detect subjects with excessive motion we calculated the total displacement parameter from the six motion parameters obtained during the realignment step. The Motion Fingerprint toolbox (Wilke, 2014, 2012) was used to produce a single motion indicator for the total displacement over time for each subject. We used the implemented standard cortical distance (d_{avg}) of 65mm. Subjects were excluded if they moved more than one voxel size (TD>3mm; Johnstone et al., 2006; Wilke, 2012).

First-level analysis was conducted using a general linear model (GLM), based on a 30s boxcar function convolved with a canonical hemodynamic response-function (hrf). High and low frequency block onsets were modelled in separate regressors. Fixation blocks were not modelled and formed the implicit baseline (Meyhöfer et al., 2015). The six motion regressors from the realignment procedure were entered as covariates of no interest.

Group-level statistics were performed by a second-level random effects full factorial design with Frequency (0.2Hz and 0.4Hz) as within-subject factor and Group (methylphenidate, nicotine and placebo) as between-subject factor. The motion parameter TD was included as a covariate of no

interest. Task activation was obtained from the contrast pursuit>baseline and frequency activation was obtained by the contrast high>low (Meyhöfer et al., 2015).

We first performed an omnibus F-test to detect clusters showing a drug effect at whole brain level. Significant clusters in *post-hoc* group comparisons between methylphenidate and placebo, nicotine and placebo, and methylphenidate and nicotine were only interpreted if the F-test survived the statistical threshold after multiple comparison over the whole brain ($p<0.05$, family-wise-error corrected at peak level).

We further investigated combined drug effects with a conjunction analysis. This analysis aimed to identify consistently high and jointly significant structures for nicotine and methylphenidate compared to placebo. We performed a conjunction analysis of the minimum T-statistic over the contrasts methylphenidate>placebo and nicotine>placebo as implemented in SPM8 (Friston et al., 2005; Nichols et al., 2005). Significant clusters describe effects that are significant in both drug conditions against placebo.

Additionally, to be more sensitive for task-specific drug effects we performed a region-of-interest (ROI) analysis. The ROI consisted of clusters that were significantly activated during smooth pursuit. The pursuit activation ROI mask was obtained from an independent sample from a previous study who had performed the same task in the same scanner (Meyhöfer et al., 2015). The mask contains all clusters listed in Table III in Meyhöfer et al. (2015; k=19915 voxels; N=31).

For second-level analyses, significant clusters were inferred if the peak voxel of the cluster survived a statistical threshold of $p<0.05$ family-wise-error (FWE) corrected.

Anatomical labels were defined with the WFU Pickatlas Version 3.0.5 (Maldjian et al., 2004, 2003) and the updated version of the Automated Anatomical Labeling Atlas AAL2 (Rolls et al., 2015; Tzourio-Mazoyer et al., 2002). Functional localizations were identified from previous literature (Dieterich et al., 2009; Herweg et al., 2014; Meyhöfer et al., 2015; Nagel et al., 2012).

Percent signal change scaled to local mean signal for relevant clusters was extracted using MarsBaR (http://marsbar.sourceforge.net).

3. Results

3.1 Subjects

After the screening procedure, eighty-two subjects were invited to the MRI facilities. One subject had to withdraw participation due to nausea after application of the dermal patch (nicotine). Thirteen subjects were excluded from further analysis due to high oculomotor signal drop out. Reasons for this were bright or squinted eyes or movement during the task which made it difficult for the camera to maintain a stable signal. Four subjects were excluded due to excessive motion (TD ranged from 3.24 to 10.04mm).

The final sample consisted of sixty-four right-handed males (mean±st.d.; age: 24.58± 3.71; height in cm: 183.42±6.30; weight in kg: 79.30 ±8.54; MWT-B score: 30.45±2.94). There were no significant group differences for TD ($p>0.97$). The mean TD values are given in Table 1 with demographics and verbal intelligence scores according to group. A chi-square test was performed to examine the relation between guessed substance (after scanning procedure) and received substance. The relation was not significant (X^2 (6, N=64)=9.11, p=0.17), which suggests that subjects were not aware of the administered compound.

3.2 Behavioural Data

Behavioural data met normality assumption. In the high frequency condition subjects made significantly more saccades ($F(1,61)=282.79$, $P<0.001$; $\eta^2_P=0.82$), had higher RMSE mean scores ($F(1,61)=318.37$, $P<0.001$; $\eta^2_P=0.84$) and lower mean maintenance gain ($F(1,61)=134.70$, $P<0.001$; $\eta^2_P=0.69$) than in the low frequency condition.

There were no other main effects or interactions for any dependent variable ($P>0.20$).

3.3 fMRI Data

3.3.1 Task activation

Pursuit blocks elicited higher BOLD activation compared to fixation in a large cluster in the occipital lobe which expanded across primary visual and motion-sensitive areas and extended into superior parietal lobule. This large cluster merged with bilateral activation in the precentral gyrus encompassing frontal and supplementary eye fields. Subcortical activation was observed in bilateral thalamus and putamen. Peak voxel of clusters are listed in Table 2 and the activation map is given in Supplementary Material (Figure S1). Effects of stimulus frequency (high>low) were located in primary visual cortices (Table 2).

3.3.2 Group effects

Significant cluster of the omnibus F-test served as inclusive mask for *post-hoc* drug comparisons. There was a main effect of group in the left precentral gyrus, in a region corresponding to the frontal eye field (FEF) (Table 3). The group effect was mediated by a significant difference in activation between the methylphenidate and the nicotine group, with the nicotine group exhibiting lower BOLD during pursuit compared to the methylphenidate group (Table 3). The

activation level of the placebo group was intermediate and did not differ significantly from either drug group. The ROI analysis confirmed this effect but revealed no additional clusters with drug effects.

There were no clusters showing an interaction between group and frequency. There were no clusters surviving statistical significance thresholds in the conjunction analysis at whole brain or within ROI mask.

3.4 Behavioural Associations with BOLD activation

We explored possible brain-behaviour associations using correlations between pursuit performance variables and the extracted mean percent signal change of the left FEF cluster. The correlations are given in Table 4. Both methylphenidate and placebo groups showed a strong positive correlation between BOLD signal and RMSE score ($r>0.4$). The nicotine group did not follow this pattern, it even seems that in the nicotine group the behavioural association was reversed (Table 4). The coefficients for the methylphenidate ($z=2.99$; $p=0.03$) and placebo ($z=3.15$; $p=0.02$) groups differed significantly from the nicotine group during low frequency blocks. The same pattern was observed during high frequency blocks, although the difference was only significant between methylphenidate and nicotine ($z=2.33$; $p=0.02$). Maintenance gain was positive correlated with BOLD in the nicotine group, though this was only observed in the low frequency condition. Saccade frequency was positively correlated with BOLD signal in the placebo group, specifically in the low frequency group. However, after correction for multiple analyses, none of the listed correlations survived the statistical threshold ($p<0.002$).

4. Discussion

Nicotine and methylphenidate are considered to be putative cognitive enhancers. Meta-analyses of healthy, non-sleep deprived human subjects have identified both compounds to increase performance in several cognitive domains (Heishman et al., 2010; Linssen et al., 2014). Although there may be ethical concerns surrounding the issue of cognitive enhancement (Hyman, 2011), it is of considerable scientific interest to further investigate the potential of biotechnological interventions to enhance human cognition. One of the aims of such investigations is to increase knowledge on the specific and shared neuronal underpinnings of enhancing compounds. Both nicotine and methylphenidate have been shown to enhance overlapping measures of attentional performance (Bizarro et al., 2004; Levin et al., 2001) and smooth pursuit (Allman et al., 2012; Sherr et al., 2002). Here, for the first time we directly compared the effects of these two compounds on smooth pursuit performance and brain function.

On the behavioural level, we did not observe an enhancing effect of either compound on the key behavioural measures of smooth pursuit, namely maintenance gain, saccadic frequency or mean RMSE.

Several studies have found beneficial effects of nicotine on smooth pursuit performance in smokers (Dépatie et al., 2002; Domino et al., 1997; Klein and Andresen, 1991; Olincy et al., 1998), but not in non-smokers (Avila et al., 2003; Schmechtig et al., 2013). This suggests that previous findings of nicotinic enhancement may have been confounded by the operation of withdrawal effects. It should also be noted that some studies found adverse effects of nicotine on smooth pursuit performance (Sibony et al., 1988; Thaker et al., 1991).

We also did not find an effect of methylphenidate on smooth pursuit performance with the current dosage (corresponding to a range from 0.43 to 0.62mg/kg), whilst in a previous study with lower dosage (corresponding to an average of 0.26mg/kg) we observed a significant increase in maintenance gain and a significant reduction in saccadic frequency (Allman et al., 2012). The current dosage has been shown to improve performance in more challenging visual tasks (Finke et al., 2010), but has the lowest proportion of effects on cognition in healthy samples compared to medium and low dose (≤20mg) (Linssen et al., 2014). Following from these arguments, we would predict that a 40mg dose may improve smooth pursuit performance in a more challenging variant of the task, e.g. at higher target frequencies or when using the blanking paradigm (Barnes, 2008). Additionally, an even higher dosage might be associated with decreased task performance following an inverted-u shape drug response curve (Cools and D'Esposito, 2011).

The absence of performance enhancement in the current sample could also derive from individual performance differences in drug response. There is evidence that significant drug effects may be limited to certain subgroups, such as groups with low baseline performance (Petrovsky et al., 2012) or specific genetic variation (Bellgrove et al., 2005). However, Allman et al. (Allman et al., 2012) did not find baseline dependent effects in the modulation of methylphenidate for smooth pursuit.

On the neural level, nicotine reduced frontal eye field (FEF) activation in comparison to methylphenidate. Interestingly, we previously observed a reduction in left FEF activation in non-smokers after nicotine injection compared to placebo during another oculomotor biomarker, the antisaccade task (Ettinger et al., 2009). The FEFs are a key region in the control of eye movements. During pursuit the FEFs are thought to regulate pursuit maintenances and also initiation and prediction of target movement (Lencer and Trillenberg, 2008). The FEFs receive

subcortical input from superior colliculus and substantia nigra (Lynch et al., 1994). Cholinergic stimulation of superior colliculus leads to improved initiation of eye movements (Aizawa et al., 1999), whereas electrical stimulation of substantia nigra operates bidirectionally and either suppresses or enhances pursuit movement (Basso et al., 2005). While these structures are potential action sites of the present pharmacological challenge, on the basis of our findings their involvement in the observed drug effect remains suggestive.

Previous studies have also observed regional BOLD reductions following nicotine. For example, reduced cue-related BOLD response in parietal cortex following nicotine administration has been observed in selective attention paradigms (Giessing et al., 2006; Thiel et al., 2005). Connectivity analysis with resting-state fMRI has revealed more efficient information transfer with a single dose of nicotine (Wylie et al., 2012). Together, these and our own findings point to a similar pattern of neural effects of nicotine in reducing task-related BOLD

A reduction in BOLD following nicotine administration may reflect increased processing efficiency. According to Poldrack (2015), neural cost-efficiency is apparent when the same neural computation is performed with identical time and intensity, but group differences occur in metabolic measures. Therefore, we cautiously interpret our present finding of reduced BOLD in face of similar performance in the nicotine group as more efficient processing (Poldrack, 2015). Of course this interpretation rests on the assumption that in all three groups the same neural computation is performed. Given that we observed a highly stable task network, the same stimulus frequency effects and comparable pursuit performance levels across the three groups of this study and as in other independent samples (Meyhöfer et al., 2015), we conclude that the observed difference in left FEF activation is not due to group differences in the types of computations performed. Of course it should be pointed out that further data concerning the

molecular mechanisms that might underlie the observed BOLD effect of nicotine are required in order to further bolster the proposed efficiency argument (Poldrack, 2015). Molecular imaging methods such as positron emission tomography (PET) as well as *in vivo* animal studies will be needed to answer this important question.

However, despite this converging evidence of nicotine effects on enhancing neural processing efficiency (Ettinger et al., 2009; Giessing et al., 2006; Thiel et al., 2005; Wylie et al., 2012), it is important to note that other studies have shown nicotine-induced *increase* of BOLD response in other brain areas combined with improved performance on relatively more demanding tasks (Kumari et al., 2003). Thus, there is likely not a single or consistent neural signature of nicotine; instead, its measureable effects on BOLD may depend on task characteristics and whether or not effects on performance are observed.

An additional interpretation of the significant difference between the nicotine and methylphenidate groups concerns the effects of methylphenidate on enhancing task-related activations, as observed in response inhibition (Costa et al., 2013; Nandam et al., 2014) and working memory (Tomasi et al., 2011). Activation of the FEFs, as observed more strongly in our methylphenidate group compared to the nicotine group, has been associated with spatial attention (Corbetta et al., 1998) and the voluntary control of eye movements (Pierrot-Deseilligny et al., 2004). An enhancement of such task-related activation would be in line with previously demonstrated effects of methylphenidate on task saliency (Farr et al., 2014; Linssen et al., 2014; Volkow et al., 2005). Increased activation of parietal and frontal eye fields has also been observed in tasks requiring suppression of visual background distractors (Kimmig et al., 2008; Ohlendorf et al., 2010). In one study this was accompanied by worse maintenance gain when the distractors were stationary and therefore conflicted with target movement (Ohlendorf et al.,

2010). This suggests that increased recruitment of attentional resources is required by tasks with more demanding attentional focus, but such additional recruitment of resources may not necessarily result in beneficial effects on task performance.

The correlation analysis with the FEF cluster suggests that higher BOLD is accompanied by less accuracy in pursuit. While this pattern was observed in the methylphenidate and placebo groups, nicotine seemed to change this association. Bearing in mind that BOLD activation for the nicotine group was lower than in the other groups, we would suggest that inter-individual differences in response to nicotine are responsible for the reversed correlation (Ettinger et al 2009). The absence of significant correlations after multiple comparison correction and the lack of previous reports on correlation of FEF activity and RMSE score, however, make it difficult to conclusively interpret this finding.

4.4 Limitations

Some limitations of the present study should be noted. The conclusions drawn are limited to healthy male non-smokers. Although this selection strategy maximizes sample homogeneity and avoids influences of potential hormonal fluctuations in females or nicotine withdrawal effects in smokers, it comes at the cost of reduced generalizability (Devito et al., 2013; Jasinska et al., 2014). An additional limitation of the study is the comparability of the stimulant dosage in relation to previous studies. Whilst we administered dosages that modulate the targeted neurotransmitter systems and that have been successfully employed in previous studies, we have no objective measure to what extent we challenged the relevant neurotransmitter systems at an individual basis. Further investigations would benefit from dosage variations in order to illustrate true inverted u-shaped effects. Additionally, measures of receptor occupation would be

informative with regards to the important issue of inter-individual drug response variability. Suitable methods include single photon-emission computed tomography (SPECT) and PET.

5. Conclusions

Overall, the application of pharmacological fMRI is sensitive to detect distinct effects of nicotine and methylphenidate on task-relevant networks. In line with the previous literature, nicotine reduced activation without worsening performance, a pattern which may be interpreted as more efficient processing (Newhouse et al., 2011; Wylie et al., 2012), whereas the increase in activation in absence of performance improvement under methylphenidate could be interpreted in the context of task saliency (Volkow et al., 2005).

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Table 1. Demographics and performance variables according to treatment group

	Methylphenidate (N=23)		Nicotine (N=21)		Placebo (N=20)	
Age in years	24.7±3.74		23.52±3.23		25.55±4.07	
Height in cm	182.0±6.34		183.43±6.38		185.40±5.86	
Weight in kg	78.74±7.17		80.23±7.69		80.00±10.75	
MWT-B score	30.38±2.46		30.10±3.53		30.95±2.82	
TD	1.16±0.75		1.21±0.62		1.27±0.55	
	0.2Hz	0.4Hz	0.2Hz	0.4Hz	0.2Hz	0.4Hz
Saccade N/sec	0.48±0.35	1.23±0.50	0.67±0.41	1.35±0.60	0.45±0.31	1.18±0.56
Maintenance Gain %	90.79±10.24	81.46±11.29	91.10±7.10	84.54±7.11	92.04±8.89	82.57±14.70
RMSE Score	56.30±11.91	93.92±14.18	53.81±17.61	84.79±20.71	56.97±16.70	90.05±20.62

Data represent mean±standard deviation; MWT-B: Mehrfachwahl-Wortschatz-Test; RMSE: root mean square error; TD = total displacement (motion indicator)

Table 2. BOLD response during pursuit>baseline and high>low across all subjects (N=64)[a]

Anatomical Label (*Functional Label)*	MNI Coordinates (x, y, z)			Cluster Size (k)	T
Pursuit>Baseline					
Calcarine cortex left *(V1)*	-8	-82	4	41189	33.50
Calcarine cortex right *(V1)*	12	-80	4		30.93
Lingual gyrus right	6	-84	-2		28.69
Superior occipital gyrus right	20	-84	26		17.33
Middle occipital gyrus left *(V5)*	-44	-72	4		20.34
Middle temporal gyrus right *(V5*)	48	-66	2		16.27
Precentral gyrus left *(frontal eye field)*	-42	-8	52		18.75
Precentral gyrus left *(frontal eye field)*	-36	-10	48		17.71
Superior temporal gyrus right	62	-36	20	331	8.83
Medial cingulate left	-12	-22	42	307	16.46
Putamen right	24	-4	8	172	7.45
Middle frontal gyrus left	-46	50	-10	160	6.99
Precentral gyrus left	-46	0	10	32	6.02
Posterior orbitofrontal cortex right	36	22	-22	15	5.17
Frontal medial orbitofrontal cortex left	-2	56	-12	10	5.03
Cerebellum left	-36	-40	-34	53	8.85
High>Low					
Calcarine cortex right *(V1)*	16	-68	12	4242	5.18
Calcarine cortex left *(V1)*	0	-84	10		5.07

MNI= Montreal Neurological Institute

[a]Whole brain voxel-wise FWE (family-wise error) corrected (*P*<0.05).

Table 3. Group effects on BOLD response (N=64)[a]

Anatomical label (*Functional Label)*	MNI Coordinates (x, y, z)			Cluster Size (k)	
Group Effects at Whole Brain					
Main Effect of Group					
Precentral gyrus left (*frontal eye field)*	-38	-10	46	75	F=15.55
Methylphenidate>Nicotine					
Precentral gyrus left (*frontal eye field)*	-38	-10	46	75	T=5.57

MNI= Montreal Neurological Institute

[a]peak voxel threshold (P_{FWE}<0.05)

Table 4. Correlations between BOLD and smooth pursuit performance

	RMSE Score		Maintenance Gain %		Saccade N/sec	
FEF BOLD Signal Change	0.2Hz	0.4Hz	0.2Hz	0.4Hz	0.2Hz	0.4Hz
Methylphenidate (N=23)	0.47*	0.47*	-0.32	-0.07	0.02	-0.08
Nicotine (N=21)	-0.43	-0.27	0.45*	-0.08	-0.38	0.03
Placebo (N=20)	0.54*	0.25	-0.22	-0.05	0.48*	0.10

Data represent Pearson's r correlation coefficient; FEF: cluster with main effect of group in left precentral gyrus; *correlation significant at $p<0.05$. Note: no significant correlations after Bonferroni correction

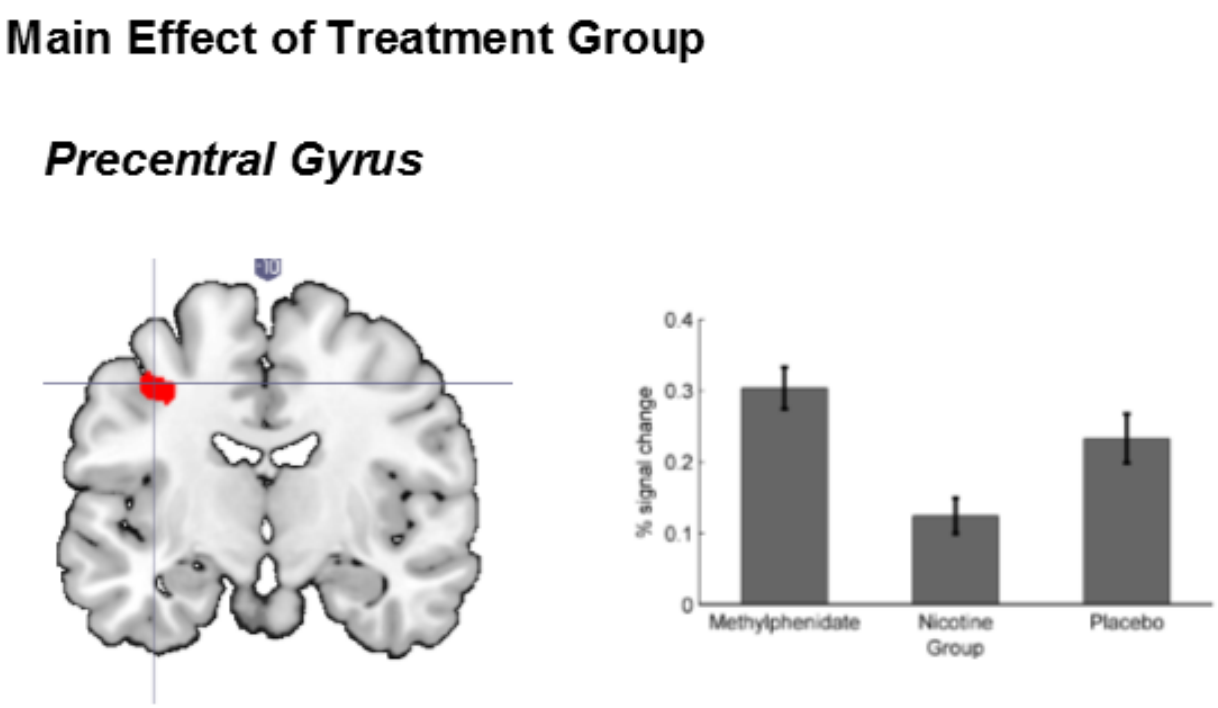

Figure 1. Group effect on BOLD ($p<0.05$ FWE corrected) and local percent signal change. Error bars depict standard error of the mean. Cross hair marks peak voxel MNI coordinate (x=-38; y=-19, z= 46). Left is left side.

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Highlights

- A pharmacological eye-tracking fMRI study was performed to investigate neural and performance effects of psychostimulants in eighty-two healthy male non-smokers
- We used a smooth pursuit paradigm with sinusoidal target movement to investigate performance and BOLD effects of nicotine and methylphenidate
- There was no influence on behavioural measures of pursuit eye movement
- On neural level, the methylphenidate group exhibited increased left frontal eye field
- activation in contrast to the nicotine group