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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 (7 mg nicotine patch and placebo capsule), or methylphenidate (placebo patch and 40 mg 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, with an intermediate response under placebo.
Discussion: The reduced activation of task-related regions under nicotine could be associated with more efficient neural processing, while increased hemodynamic response under methylphenidate is interpretable as enhanced processing of task-relevant networks. Together, these findings suggest dissociable neural effects of these putative cognitive enhancers.

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

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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.

Methods and materials

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.

Design and procedure

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

The administered dosage of 40 mg 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 min (Swanson and Volkow, 2002; Volkow, 1995; Volkow et al., 2001), therefore subjects were scanned 1 h after capsule administration. The identical looking placebo capsule contained lactose.

A 7 mg transdermal nicotine patch (NiQuitin Clear 7 mg, 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 3 h 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, 4.8 mg, Hansaplast, Germany). Placebo patches were cut to the approximate size of the nicotine patches (3×2 cm).

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 2 h 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,