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DIFFERENCES BETWEEN NICOTINE-ABSTINENT SMOKERS AND NON-SMOKERS IN TERMS OF VISUOSPATIAL ATTENTION AND INHIBITION BEFORE AND AFTER SINGLE-BLIND NICOTINE ADMINISTRATION

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Abstract—The cholinergic system is implicated in visuospatial attention and inhibition, however the exact role is still unclear. Two key mechanisms in visuospatial attention are bias and disengagement. Bias refers to neuronal signals that enhance the sensitivity of the sensory cortex, disengagement is the decoupling of attention. Previous studies suggest that nicotine affects disengagement and (related) inhibition. However the exact relation is still unknown. Furthermore, nicotine-abstinence in 'healthy' smokers may resemble some anomalies of visuospatial attention and inhibition as seen in Attention Deficit/Hyperactivity Disorder (ADHD). Smokers and non-smokers (32 male students) performed in a visuospatial cueing (VSC) task, to assess bias and disengagement, and in a stop-signal task (SST) to assess inhibition. It was expected that nicotine abstinent smokers compared to non-smokers, would show poor disengagement (indicated by an enhanced validity effect) and poor inhibitory control (indicated by an enhanced stop-signal reaction time (SSRT)). It was expected that nicotine would positively affect disengagement and inhibition: hypothesis 1 stated that this effect would be larger in smokers as opposed to non-smokers, in terms of smoking-related deficient inhibitory control. Hypothesis 2 stated the exact opposite, in terms of drug-tolerance. Results indicated no baseline differences. Nicotine enhanced inhibition more in non-smokers relative to smokers. Integrating the results, nicotine-abstinent smokers do not seem to resemble ADHD patients, and do not seem to smoke in order to self-medicate a pre-existing deficit pertaining to mechanisms of visuospatial attention and inhibition. Nicotine may affect inhibition more in non-smokers relative to smokers, consistent with a drug-tolerance account. © 2014 Published by Elsevier Ltd. on behalf of IBRO.

Key words: nicotine, attention, inhibition, ADHD, cholinergic, acetylcholine.

INTRODUCTION

Nicotine facilitates cholinergic neurotransmission (Wonnacott et al., 1990), and benefits cognitive performance in smokers and non-smokers (Rezvani and Levin, 2001; Potter and Newhouse, 2004; Froeliger et al., 2009; Heishman et al., 2010). For example the increase in cholinergic neurotransmission after nicotine administration has been implicated to affect (visuospatial) attention and inhibition (Witte et al., 1997; Potter et al., 2012), although the exact role of acetylcholine is still unknown. A better understanding of the role of cholinergic neurotransmission in attention and inhibition may fuel treatment for pathologies in which these mechanisms play a role. One disorder in which attention and inhibition are negatively affected is Attention-Deficit/Hyperactivity Disorder (ADHD) (Kenemans et al., 2005). Interestingly, smoking is correlated with ADHD, which is marked by anomalous functioning of mechanisms of attention and inhibition and it has been suggested that ADHD patients smoke to self-medicate and thus compensate for some of the pathology (Kollins et al., 2005; Potter et al., 2006). It is tempting to suggest that nicotine abstinent smokers may, in some way resemble (sub-clinical) ADHD patients. Some recent studies support this idea. Several studies show neurocognitive deficits in attention and response inhibition (key deficits of ADHD) in nicotine-deprived smokers (Ashare et al., 2014). Furthermore, nicotine-deprived smokers show prefrontal hypoactivity (de Ruiter et al., 2012) and abstinence modulates right Inferior Frontal Gyrus activity (Kozink et al., 2010), a region important in response inhibition and negatively affected in ADHD (Pliszka et al., 2007).

Firstly, the aim of the present study was to assess potential differences between smokers and non-smokers in terms of baseline measures of visuospatial attention and inhibition and in terms of the acute effect of nicotine on these measures. Secondly, the aim was to gain a

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Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; EEG, electroencephalography; nAChRs, nicotinic acetylcholine receptors; POMS, Profile of Mood States; RT, reaction time; SOA, Stimulus Onset Asynchrony; SSRT, stop-signal reaction time; SST, stop-signal task; VSC, visuospatial cueing.

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more thorough understanding of the role of acetylcholine in visuospatial attention and inhibition.

Two mechanisms are of crucial importance in visuospatial attention: bias and disengagement (Corbetta and Shulman, 2002; Corbetta et al., 2008). Bias refers to neuronal signals that modulate the sensitivity of the sensory cortex and the ensuing enhanced neural processing of the stimulus to which attention is directed to. Disengagement refers to the decoupling of attention. A classic paradigm to investigate visuospatial attention is the visuospatial cueing (VSC) task (Posner et al., 1980). In this task a cue points to the right or left visual hemifield. In the majority of trials, a target, to which a response is required, is presented at the cued location. The benefit of cueing in terms of reaction time (RT) of valid cueing is termed the validity effect. Nicotine reduces the validity effect (Meinke et al., 2006; Thiel and Fink, 2008; Vossel et al., 2008). More specifically, for both smokers and non-smokers, nicotine seems to reduce RTs on invalid trials, suggesting a facilitation of disengagement (Witte et al., 1997; Meinke et al., 2006; Thiel and Fink, 2008). One isolated electroencephalography (EEG) study seemed to support this and suggested a possible effect of nicotine on disengagement-related electrophysiological activity, but this result was not described in detail and seemed post hoc (Meinke et al., 2006). It should be noted that a reduction of the behavioral validity effect may theoretically also imply reduced bias. Indeed, Impey et al. (2013) reported a nicotine-induced modulation of the P1 in valid trials in non-smokers. However, the P1 was increased, not decreased which may seem to contradict previous behavioral results in that a reduced behavioral validity effect implies a reduced attentional bias. It should be noted here, that the reported effect pertained to the P1 (specifically on valid trials), not to the P1 effect (the enhanced P1 on valid trials as opposed to invalid trials). Although the effect on the P1 is interesting and seems to fit an account in terms of sensory facilitation, it does not specifically fit an interpretation in terms of attentional bias (also see Meinke et al. (2006)). One issue in Impey et al. (2013) was that the main effect of cue (valid versus invalid) pertaining to RT was not significant, posing a question with respect to the reliability and success of the attentional manipulation. Importantly, if RT is not significantly modulated by cueing (valid versus invalid), then the absence of any effect of nicotine on this modulation (or EEG reflections hereof) is not surprising. It must also be noted that functional magnetic resonance imaging (fMRI) studies also fail to support the notion of a nicotine-induced effect on bias, as no effect of nicotine was evident on the attentional modulation in the occipital cortex (Thiel and Fink, 2008; Vossel et al., 2008).

Inhibition has been investigated with the stop-signal task (SST). In the SST, go stimuli are presented to which a response is required. In a minority of trials, the go stimulus is followed by a stimulus signaling to withhold the prepotent response. The behavioral outcome, the stop-signal reaction time (SSRT), is thought to reflect inhibitory motor control. There is a conceptual link between inhibition and disengagement, which has both an anatomical and a pharmacological substrate. Inhibition (as indexed by the SSRT) is negatively affected by disruptions of the right Inferior Frontal Gyrus (Aron et al., 2003), the same region has been associated with disengagement and reorienting of attention (Corbetta and Shulman, 2002; Corbetta et al., 2008). Indeed, nicotine effects on inhibition mirror those on disengagement. In the SST, nicotine has been shown to reduce the SSRT in non-smoking ADHD patients, indicating improved inhibition (Potter and Newhouse, 2004, 2008; Potter et al., 2012) and, as mentioned before, in healthy (non-smoking and smoking) participants nicotine decreases RTs on invalidly cued targets in the VSC task, indicating facilitated disengagement. It should be noted that effects of nicotine may depend on baseline performance. Results of Potter et al. (2012) indicate that the reduction of SSRTs in response to nicotine may be restricted to groups with poor inhibitory control. Potter et al. (2012) compared nonsmoking ADHD patients with relatively long SSRTs to healthy nonsmoking controls with respect to the effect of nicotine on SSRT. Nicotine reduced SSRTs only in the ADHD group, indicating facilitated inhibition only for slow stoppers. We argued that nicotine-deprived smokers may present with deficient inhibitory control and the obvious hypothesis follows that the acute effect of nicotine would be enhanced in nicotine abstinent smokers as opposed to non-smokers. Alternatively, it has been argued that smokers show drug-tolerance (Srivastava et al., 1991). This would lead to the hypothesis that nicotine asserts a stronger effect in non-smokers than in (nicotine abstinent) smokers (alternative hypothesis 2).

In sum, smoking has been associated with ADHD, which is marked by deficits in bias, disengagement and inhibition. Nicotine seems to positively affect both disengagement and inhibition. As mentioned before, the size of this effect may be stronger when baseline functioning is lower and hence, when there is poor inhibitory control, such as in ADHD patients. Possibly, nicotine abstinent smokers resemble ADHD patients in terms of (subclinical) deficits of disengagement and inhibition that may be compensated by smoking. In line with this notion, this group as compared to non-smokers would show a stronger nicotine-induced effect (hypothesis 1). On the other hand, in terms of drug-tolerance, it may be that nicotine would assert a stronger effect in non-smokers (hypothesis 2).

The two hypotheses are tested in the current study in which 16 smokers and 16 nonsmokers performed in a VSC task and SST task in a prepost, single-blind, placebo-controlled, crossover experimental setup. It was hypothesized that on baseline, smokers would have a longer SSRT and a larger validity effect as opposed to nonsmokers. Furthermore, hypothesis 1 states that the acute effect of nicotine on these parameters would be larger (reduction of the validity effect and decrease of SSRT) in smokers as opposed to nonsmokers. Hypothesis 2 states the exact opposite of hypothesis 1.