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Acute effects of nicotine on attention and response inhibition

E.M. Bekker [a,*], K.B.E. Böcker [a], F. Van Hunsel [a], M.C. van den Berg [a], J.L. Kenemans [a,b]

[a] Department of Psychopharmacology, Utrecht University, The Netherlands
[b] Department of Psychonomics, Utrecht University, The Netherlands

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Abstract

Smoking is highly prevalent among patients with Attention Deficit Hyperactivity Disorder (ADHD). Previous studies using the reversed continuous performance task (R-CPT) have suggested that nicotine reduces inattention. Since especially adults with ADHD have been claimed to suffer from a core deficit in inhibitory control, this study aimed at determining whether nicotine improves response inhibition in addition to attention. Sixteen healthy regular smokers participated in a pre/post treatment design in which transdermal patches containing 7 and 21 mg nicotine per day were administered in a counterbalanced, double-blind manner. In a second study, patches containing 0 mg (placebo) and 21 mg per day were administered to a different group of regular smokers. For replication purposes, the R-CPT and the profile of mood states (POMS) were administered. Furthermore, a different version of the continuous performance task (CPT-AX) and the stop-signal task, traditionally used to measure response inhibition, were presented. The high dose of nicotine was found to relieve self-reported Depression in Study 1 and Fatigue in Study 2. Performance data indicated acute effects of nicotine on attention-related, but not on inhibition-related measures. Especially the comparison with placebo revealed decreases in reaction time and variability of responding. The results imply that patients with ADHD smoke to reduce inattention.

Keywords: Continuous performance task; Stop-signal task; Nicotine; Transdermal patch; Attention; Response inhibition; POMS

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a psychiatric disorder characterized by symptoms of inattention, impulsivity, and hyperactivity (APA, 1994). Although this disorder has long been thought to be restricted to childhood, longitudinal studies have suggested that at least one- to two-thirds of the affected children do not outgrow their problems (Weiss et al., 1985; Barkley et al., 2002). In adulthood, patients with ADHD seem inclined towards smoking. Approximately 40% of the adults with ADHD smoke cigarettes compared to about 26% in the general population (Pomerleau et al., 1995; Coger et al., 1996). Alarmingly, adolescents with ADHD also have an increased risk to engage in this health threatening habit (Milberger et al., 1997; Lambert and Hartsough, 1998). Smoking has been hypothesized to reflect a form of self-medication in patients with ADHD (Levin et al., 1996a). If so, nicotine skin patches, being less harmful to ones health than cigarettes, might be employed for treatment of ADHD. Indeed, patch treatment has been shown to reduce ADHD symptoms as measured with the Clinical Global Impressions Scale (Conners et al., 1996; Levin et al., 1996a, 2001) and the Conners Parent Rating Scale (Shytle et al., 2002). Furthermore, specific nicotinic agonists, such as ABT-418, have been found to alleviate ADHD symptoms (Wilens et al., 1999).

Cognitive effects of nicotine include the reduction of inattention and the improvement of learning and memory (e.g., Peeke and Peeke, 1984; West and Hack, 1991; Warburton, 1992; Levin, 1992; Wesnes and Parrott, 1992; Sacco et al., 2004; Mansvelder et al., 2005). Improvements in attention involve an increase in vigilance performance and information processing speed (e.g., Wesnes and Warburton, 1983, 1984; Foulds et al., 1996; Lawrence et al., 2002). Although results are mixed, nicotine effects on divided and selective attention are generally assumed to be negligible (e.g., Heishman et al., 1994; Mancuso et al., 1999b; Rusted et al., 2000). The way in which nicotine exerts these cognitive effects

* Corresponding author. University of California, Center for Mind and Brain, 267 Cousteau Place, office 107, Davis, CA 95616 USA. Tel./fax: +1 530 297 4400.
E-mail address: embekker@ucdavis.edu (E.M. Bekker).

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has not been unraveled yet. The intake of nicotine directly stimulates acetylcholine (Ach) receptors and promotes the release of several other neurotransmitters, such as dopamine (DA), norepinephrine (NE), serotonin and GABA (Wonnacott et al., 1989). Since the most effective drug treatment for ADHD (methylphenidate) also functions as a DA agonist (by inhibiting DA re-uptake in the synaptic cleft), especially nicotinic interactions with DA have been claimed to underlie reductions in ADHD symptoms (Levin et al., 1996a; Rezvani and Levin, 2001).

The need for nicotine is not specific to ADHD: it has been found in a wide variety of psychiatric populations (e.g., Hughes et al., 1986; Mihailescu and Drucker-Colin, 2000; Thorsteinsson et al., 2001; Sacco et al., 2004; Singh et al., 2004; Newhouse et al., 2004a,b). Presumably, these patients are all striving for relief of some kind of attentional deficit or memory problem. Although inattention is one of the symptoms characterizing ADHD, we questioned whether this is indeed the main reason why patients with ADHD smoke. In children with ADHD, a lack of inhibitory control rather than a deficit in attention has been claimed to be the core deficit underlying all other symptoms (Barkley, 1997; Quay, 1997). In other words, a primary deficit in inhibition might mediate a cascade of secondary deficits in other executive functions, such as attention or arousal regulation. The first studies in adults with ADHD have suggested that such a core deficit in inhibition stands out even more clearly in adults than it does in children (Lijffijt et al., 2005; Bekker et al., 2005). Accordingly, we hypothesized that an improving effect of nicotine on response inhibition might be more important in explaining the high prevalence of smokers in the ADHD population. Therefore, in the present study, we explored whether nicotine has the potential of improving behavioral measures reflecting response inhibition (in addition to attention) in healthy subjects.

Up until now, nicotine studies have mostly used the reversed version of the continuous performance task (CPT). In the original CPT (Rosvold et al., 1956), different letters are rapidly presented one by one. Subjects are instructed to press a button when the letter X (go stimulus) is presented, but to refrain from responding to all other letters (nogo stimuli). Increases in the mean reaction time (RT), the variability of responding (SDRT), and the number of missed responses (omissions) have generally been inferred to reflect deficits in sustained attention, whereas increases in the number of incorrect responses to nogo stimuli (false alarms) have been inferred to reflect deficits in response inhibition (Corkum and Siegel, 1993; Riccio et al., 2001; Castellanos and Tannock, 2002). Since subjects hardly make any false alarms in the original CPT, Conners (1995) reversed the task instruction to increase subjects' tendency to respond. In this reversed versions (R-CPT), subjects are required to respond to each letter (go stimuli) except for the letter X (nogo stimulus). Nicotine studies using the R-CPT have mostly shown effects on measures presumed to reflect attention. Decreases in reaction times, the variability of responding and the number of omission errors were reported in smokers and non-smokers with or without an ADHD diagnosis (Levin et al., 1996a,b, 1998; White and Levin, 1999; Levin et al., 2001). Only a few studies additionally reported (slight) decreases in the number of false alarms (Levin et al., 1996b, cited in Riccio et al., 2001; Levin et al., 1998; Zack et al., 2001). Other indications for nicotine effects on response inhibition involve increased false alarm rates (Hatsukami et al., 1989) and reduced oculomotor response inhibition (Powell et al., 2002) after nicotine deprivation, and increased false alarm rates after prenatal exposure to nicotine (Fried and Watkinson, 1988). As for another inhibitory competence, the ability to suppress interference (Nigg, 2000), administration of nicotine has been found to reduce eye movements to task irrelevant stimuli (Rycroft et al., 2005) and to increase inhibition of unpractised exemplars on the retrieval-induced forgetting task (Edginton and Rusted, 2003). Thus, although results are mixed, nicotine seems to increase attention as well as response inhibition. The latter is partly inferred from studies showing deprivation-induced decrements in response inhibition.

In various studies, effects of nicotine have been confounded with the relief of withdrawal effects after overnight deprivation (Wesnes and Parrott, 1992). Withdrawal symptoms include negative affect, restlessness, difficulty concentrating, increased heart rate and increased appetite (Benowitz and Jacob, 1993). To exclude effects of withdrawal relief after nicotine intake, low doses of nicotine have been administered to non-smoking subjects who do not show withdrawal symptoms (Levin et al., 1998) or effects obtained in smokers have been compared to those obtained in non-smokers (Levin et al., 1996a). We administered transdermal patches containing either 7 or 21 mg nicotine per day in a pre/post treatment, counterbalanced, double-blind design to 16 regularly smoking (10–25 cigarettes per day), but otherwise healthy subjects (Study 1). Regular smokers were selected to avoid side effects in the high dose condition. A pre/post treatment design was used to reduce variance (Kenemans et al., 1999). A low dose of nicotine rather than a genuine placebo patch was used to control for the relief of withdrawal effects. The use of a low dose as a baseline for the 21 mg patch might mask nicotine effects when performance improves in both dose conditions. Therefore, we performed a control study in which transdermal patches containing either 0 (placebo) or 21 mg nicotine per day were administered to a different group of 16 regularly smoking subjects using the same experimental design (Study 2).

To gain insight into nicotine dependence, each subject filled out the Fagerström Test of Nicotine Dependence (Fagerström, 1978; Heatherton et al., 1991). For replication purposes, we presented the reversed version of the CPT and the profile of mood states (POMS) (McNair et al., 1971; Wald and Mellenbergh, 1990). Regarding self-report reflections of mood, previous studies have generally found that nicotine reduces tiredness, but enhances perceived activity level and feelings of happiness (Warburton and Mancuso, 1998; Gentry et al., 2000; Gilbert et al., 2000; Levin et al., 2001). To specifically test the hypothesis that nicotine improves response inhibition, we additionally presented two tasks that have traditionally been used to measure inhibitory control in healthy subjects as well as in patients with ADHD: the cued version of the CPT (CPT-AX) (Rosvold et al., 1956) and the stop-signal task (Logan, 1994).

To the best of our knowledge, the latter two tasks have not been presented in studies assessing the behavioral effects of nicotine in healthy subjects before.

2. Methods

2.1. Subjects

In Study 1, 16 healthy regular smokers participated (mean age=23.25 (8.24), age range=18–53, 8 males, 13 right-handed, 15.50 (4.38) cigarettes a day). The 6-item Fagerström Test for Nicotine Dependence (FTND) revealed a mean total score of 2.4 (1.64). In Study 2, a different group of 16 healthy regular smokers participated (mean age=23.19 (2.43), age range=20–28, 8 males, 16 right-handed, 15.75 (3.92) cigarettes a day). The 6-item Fagerström Test for Nicotine Dependence (FTND) revealed a mean total score of 2.2 (1.66). All subjects were recruited with advertisements on university bulletin boards and received 70 for participation. Exclusion criteria consisted of past loss of consciousness due to head injury, developmental disorder in childhood, current treatment by a healthcare professional (with special emphasis on heart problems, skin problems, kidney or liver dysfunction and intestinal problems), pregnancy, the use of psychoactive medication, and drug abuse. Prior to participation, the use of drugs (at least 3 weeks), alcohol (at least 24 h), caffeine and cacao (at least 12 h) was prohibited. To ensure comparable nicotine blood levels across dose conditions and studies, subjects were also required to abstain from smoking for at least 12 h prior to participation (overnight deprivation in regular smokers was also used by e.g., Levin et al., 1996a,b; Warburton and Mancuso, 1998; Mancuso et al., 1999a,b). All subjects claimed to have normal hearing and normal or corrected-to-normal vision and signed an informed consent written in accordance with the guidelines of the Ethics Committee of the University Medical Center Utrecht. All further procedures were in compliance with the guidelines of the review board for Scientific Research in Humans of the Utrecht University Faculty of Social Sciences.

2.2. Procedure

Each subject came to the laboratory twice. Upon arrival at 8:45 am, the use of alcohol was tested with a breath device (Alcotest, Dräger Medical, Lübeck, Germany). Although each subject was told that nicotine intake was likely to be tested as well, a breath device measuring carbon monoxide (Smokerlyzer, Bedfont Scientific Ltd., Kent, UK) was not available for the first 8 subjects in Study 1. When tested, compliance was confirmed (blood alcohol levels (bac)<.01, carbon monoxide (CO) level<10 parts per million (ppm): given the persistence of carbon monoxide in the bloodstream with overnight lack of exercise, a cut-off value of 10 ppm was used (see also Warburton and Mancuso, 1998)).

On each test day, there were two experimental sessions: the first session took place between 09:00 am and 10:00 am, and the second session took place between 04:00 pm and 05:00 pm. Within each session, first the POMS was administered. Then, three computer tasks were presented. Immediately after the first session, a covered up nicotine patch (NICOTINELL, NOVARTIS) was attached to the subject's lower back in a double blind manner (by a person not being the experimenter). The nicotine patches contained 7 or 21 mg in Study 1 and 0 (placebo) or 21 mg in Study 2. The order of dose conditions (7 mg/0 mg first or 21 mg first) was counterbalanced across subjects. After 6 h, the second session began. Patches result in steadily increasing blood concentrations without peaks and troughs (Benowitz and Jacob, 1991, 1993; Fant et al., 2000). Plasma concentrations are detectable within 1 h after application with maximum absorption between 6 and 12 h. Previous studies using NICOTINELL patches have demonstrated effects on attention related measures and the POMS after 6 h (Warburton and Mancuso, 1998). Between sessions, subjects remained in the laboratory under supervision of the experimenter. A standard lunch that did not contain caffeine, cacao or sugar was provided. As for side effects, in Study 1, two subjects reported headache. In Study 2, one subject reported headache and another subject reported itchy skin. These symptoms were mild and well tolerated. None of the subjects requested patch removal.

2.3. Tasks

Subjects were seated in a sound-attenuating room at a distance of 80 cm from a computer screen. Three tasks were presented: the reversed CPT (around 15 min), the CPT-AX (around 15 min) and the stop-signal task (around 30 min). For a given subject, the order of task presentation was the same for each of the 4 sessions. The stop-signal task was always presented as the second task. The presentation order of the two CPT tasks was counterbalanced across subjects. To increase the likelihood of impulsive responding (false alarm rates), response speed was emphasized in each task.

In the reversed CPT, 16 different white capital letters (A, B, C, D, E, F, H, I, L, M, N, O, T, X, Y, Z) were alternately presented for 250 ms against a black background. Inter-stimulus intervals (ISIs) were 1, 2, or 4 s. Subjects were instructed to press a key with the dominant response hand upon presentation of all letters except for the letter X. A practice block containing 50 trials preceded an experimental block containing 360 trials. Merely for randomization purposes, the 360 trials were subdivided into 18 blocks of 20 trials. Within each block, 2 trials contained the letter X. Each ISI occurred once every three blocks. All blocks were presented in an uninterrupted manner, i.e. without intervening pauses.

The CPT-AX and the stop signal task were designed in accordance with tasks used in previous studies with ADHD patients (Overtoom et al., 1998; Bekker et al., 2005). In the CPT-AX, 11 different black capital letters (A, B, C, D, E, F, G, H, J, L, X) were alternately presented for 150 ms between two continuously present vertical bars against a black background. Inter-stimulus intervals varied randomly between 1400 and 1600 ms. Subjects were instructed to respond with the dominant hand when the letter A (cue) was followed by the

letter X (go stimulus), but to refrain from responding to all other letter sequences. A practice block containing 60 trials preceded an experimental block containing 400 trials. The letters A, X and H appeared with a frequency of 20%. The remaining letters appeared with a frequency of 5%. The probability that a go stimulus succeeded the cue was 50%. Physically identical stimuli never succeeded. Furthermore, the letter A never followed the go sequence AX or the nogo sequence AnotX (a letter other than X following the letter A).

In the stop-signal task, a white plus-symbol was presented for 500 ms against a gray background. This warning stimulus was replaced with one out of two equiprobable square-wave, black-on-white gratings containing either a high (4.8 cpd) or a low (0.6 cpd) spatial frequency. Gratings were presented for 750 ms. Inter-trial intervals varied randomly between 1000 and 1250 ms. Subjects were instructed to press a button with the right index finger when a high spatial frequency grating was presented and to press a button with the left index finger when a low spatial frequency grating was presented. The mapping of the response hand reversed after half of the blocks. Unpredictably, on 40% of the trials, a tone (1000 Hz, 80 dB, 400 ms) was presented binaurally through earplugs. In the stop-signal task, this tone indicated that the planned response to the grating should be withheld. The delay between the grating and the tone (SOA) was adjusted with a tracking algorithm (De Jong et al., 1995) to yield a performance of around 50% successful stops that was corrected for the estimated percentage of omissions (Pic) (Tannock et al., 1989). To avoid waiting strategies induced by the predictability of the timing of the stop signal, the actual SOA was jittered in a range of 240 ms (with steps of 10 ms) surrounding the calculated SOA (Pliszka et al., 2000). First, a practice block containing 60 trials without stop signals and a practice block containing 126 trials with 40% stop trials were presented. Subsequently, four experimental blocks of 126 trials were presented. Before reversing the response hand mapping, which occurred after two blocks, a practice block containing 60 trials without stop signals was presented.

2.4. Statistical analysis

For each study and each task separately, planned comparisons of Dose (0 mg/7 mg versus 21 mg) × PrePos (pre versus post treatment measurement) were performed using repeated measures of variances containing *F*-tests (Wilks' Lambda) with a critical α-level of 0.05. The factor order (0 mg/7 mg versus 21 mg in first session) was included in the within-subject design solely to reduce its contribution to the error term. If a given effect did not significantly depend on order, this factor was removed from the model, because in this case its inclusion might decrease statistical power by the loss of degrees of freedom (*df*s=(1,14) rather than (1,15)) (Kenemans et al., 1999).

To assess effects of nicotine on attention, for each subject and each block, reaction times (RT), variability of responding (SDRT), and percentages of omissions were calculated. In addition, in the stop signal task, the percentage of discrimination errors was computed. To assess effects of nicotine on response inhibition, for each subject and each block, percentages of correct rejections and successful stops (Ps) were calculated. In the CPT-AX, correct rejections were calculated separately for cues (the letter A), nogo stimuli (AnotX), and X-only stimuli (X not preceded by the letter A). Furthermore, in the stop signal task, the stop signal reaction time (SSRT), and the delay between go stimuli and stop signals (SOA) were computed. The SSRT was estimated by weighting the percentage of failed stops (1 − Ps) with the reaction times distribution obtained for go stimuli (Logan, 1994). Changes in SSRT might reflect differences in general processing speed (i.e. attention) rather than in response inhibition (Lijffijt et al., 2005; Bekker et al., 2005). Therefore, the interaction between RT and SSRT, which enables to assess differences in processing speed that are specifically related to the processing of the tone, was additionally analyzed. Finally, the 5 subscales of the shortened versions of the POMS (Depression, Anger, Tension, Vigor, and Fatigue) were subjected to the within-subject design.

3. Results

3.1. Behavioral measures presumed to reflect attention

Fig. 1 displays mean values for the reaction time, variability of responding, and percentage of omissions and discrimination errors, separately for each task, pre/post measurement and dose condition. Error bars are displayed per condition. It should be noted that the error terms for statistical testing reflect variance in the transformed variable (High (Post minus Pre) minus Low (Post minus Pre)). Regarding Study 1 (left panel), the top panels suggest that the decrease in reaction times and the variability of responding was larger in the 21 mg condition than in the 7 mg condition in the reversed CPT and the stop signal task. Statistical analysis indicated a trend towards significance for reaction times in the reversed CPT only ($F(1,14)=4.34$, $p=.056$). The bottom panel suggests that the percentage of omissions increased in the 7 mg condition, but decreased in the 21 mg condition, whereas the increase in the percentage of discrimination errors (stop signal task only) was largest in the 21 mg condition. However, these effects did not reach significance.

As for Study 2 (right panel), the top panels suggest that the decrease in reaction times was larger in the 21 mg condition than in the 0 mg condition. Furthermore, the variability of responding decreases in the 21 mg condition, but not in the 0 mg condition. Statistical analysis confirmed this for the reversed CPT (RT: $F(1,15)=10.09$, $p<.01$; SDRT: $F(1,15)=8.90$, $p<.01$), and the stop signal task (RT: $F(1,15)=21.14$, $p<.01$; SDRT: $F(1,15)=23.43$, $p<.01$). In the CPT-AX, a significant interaction was only found for reaction times ($F(1,15)=8.28$, $p<.01$). The bottom panel suggests that the percentage of omissions increased in the 0 mg condition, but decreased in the 21 mg condition. This interaction effect was only significant in the stop signal task ($F(1,15)=5.95$, $p<.05$). The larger increase in the percentage of discrimination errors (stop signal task only) in the 0 mg as opposed to the 21 mg condition did not reach significance.

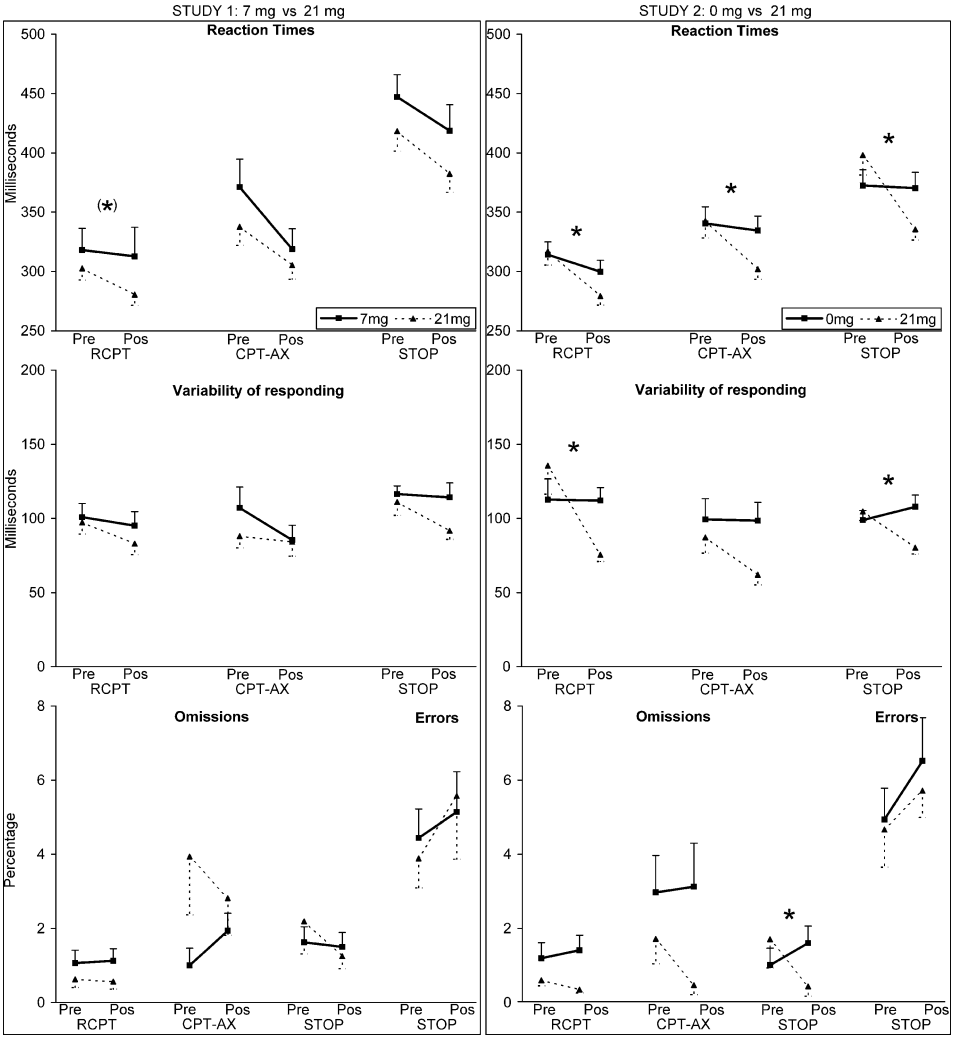

Fig. 1. Behavioral measures presumed to reflect attention obtained in Study 1 (left panel) and in Study 2 (right panel), separately for each task and pre/post measurement (see *x*-axis). Solid lines correspond to the 7 or 0 mg condition, respectively, and the dotted lines correspond to the 21 mg condition. The upper panel displays mean values for reaction times (left), the middle panel displays mean values for the variability of responding, and the lower panel displays the percentage of omission errors and discrimination errors (stop signal task only). Bars reflect standard errors. Asterisks indicate significant interaction effects. Asterisks between parentheses indicate trends towards significance.

3.2. Behavioral measures presumed to reflect response inhibition

Fig. 2 displays behavioral measures presumed to reflect response inhibition, separately for each task, pre/post measurement and dose condition. Regarding Study 1 (left panel), the top panels suggest rather mixed results for the percentage of correct rejections and successful stops. Statistical analysis only indicated a significant effect for X-only stimuli in the CPT-AX ($F(1,15)=19.29$, $p<.01$), which indicated a decrease in the 7 mg condition, but an increase in the 21 mg condition. As for the additional measures calculated in the stop signal task (bottom panel), no significant effects on SSRT, SOA or the interaction between RT and SSRT were found.

As for Study 2, the top panels again suggest rather mixed results for the percentage of correct rejections and successful stops. Statistical analysis only indicated a trend towards significance for the percentage of correct rejections in the reversed CPT ($F(1,15)=3.61$, $p=.078$), suggesting a larger decrease in the 21 mg condition than in the 0 mg condition. As for the additional measures calculated in the stop signal task (bottom panel), no significant effects on SSRT or SOA were found. The interaction between RT and SSRT was significant ($F(1,14)=4.44$, $p<.05$), and indicated an effect for RT (see under measures presumed to reflect attention), but not for SSRT.

3.3. Profile of mood states (POMS)

Fig. 3 displays mean scores derived for the 5 subscales of the short version of the POMS, separately for the pre/post measurement in each dose condition. In Study 1 (left panel), a significant effect of Dose × PrePos was only found on the subscale Depression ($F(1,15)=5.79$, $p<.05$). The increase in self-report scores of Depression was smaller in the 21 mg condition than in the 7 mg condition. In Study 2 (right panel), a significant effect of Dose × PrePos was only found on the subscale Fatigue ($F(1,14)=5.22$, $p<.05$), indicating an in-

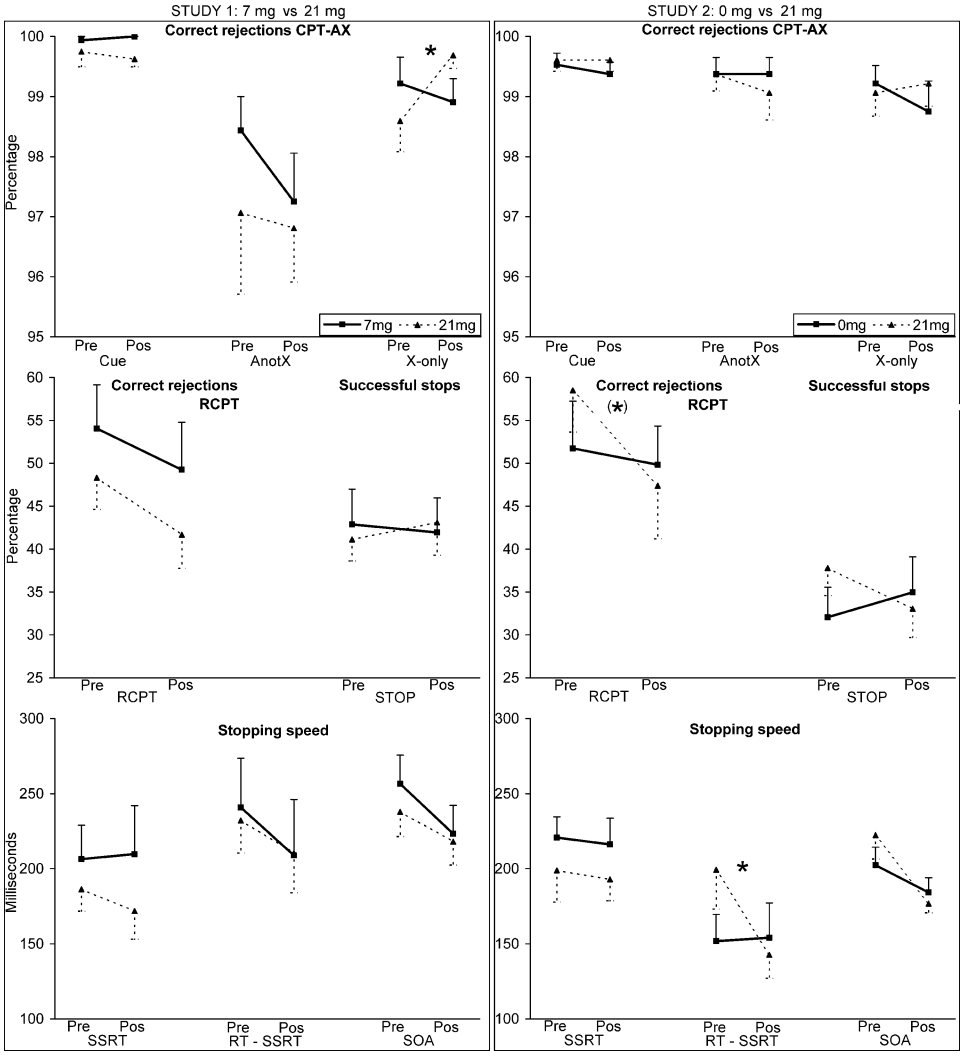

Fig. 2. Behavioral measures presumed to reflect response inhibition obtained in Study 1 (left panel) and in Study 2 (right panel). Solid lines correspond to the 7 or 0 mg condition, whereas dotted lines correspond to the 21 mg condition. The upper panel displays the percentage of correct rejections in the CPT-AX, separately for the cue, AnotX, and X-only stimulus (see *x*-axis). The middle panel displays the percentage of correct rejections in the reversed CPT (RCPT) and successful stops in the stop-signal task. The lower panel displays the stop signal reaction time (SSRT), the difference between reaction times to go stimuli and stop signals (RT-SSRT), and the delay between go-stimuli and stop signals (SOA) in the stop signal task (see *x*-axis). Bars reflect standard errors. Asterisks indicate significant interaction effects. Asterisks between parentheses indicate trends towards significance.

crease in self-report scores in the 0 mg condition as opposed to a decrease in the 21 mg condition.

4. Discussion

Nicotine has been hypothesized to serve as a form of self-medication in a variety of psychiatric populations (e.g., Levin et al., 1996a; Mihailescu and Drucker-Colin, 2000; Rezvani and Levin, 2001; Sacco et al., 2004; Singh et al., 2004; Newhouse et al., 2004a,b). Previous studies, predominantly administering the reversed CPT, have indicated that nicotine improves behavioral measures presumed to reflect attention, such as reaction times, variability of responding, and the percentage of omissions or errors (Levin et al., 1996a,b, 1998, 2001; White and Levin, 1999). We questioned whether this reduction in inattention constitutes the most important motive for smoking in adults with ADHD. Response inhibition, rather than inattention, has been claimed to be the core deficit in ADHD (Barkley, 1997; Quay, 1997), especially in adults (Lijffijt et al., 2005; Bekker et al., 2005). Therefore, this study aimed at determining whether nicotine has an improving effect on response inhibition in addition to the previously reported ameliorating effects on attention. If so, this could suggest that patient with ADHD smoke to specifically relief symptoms of impulsivity, whereas in other clinical populations smoking might more generally reduce inattention. Sixteen healthy subjects with a moderate smoking habit (10–25 cigarettes per day) participated in a pre/post treatment design. Nicotine patches containing a dose of 7 and 21 mg per day were administered in a counterbalanced double-blind manner. In this setup, differences due to relief of withdrawal effects across conditions were minimized. Since the use of a 7 mg dose as a baseline for the 21 mg condition might mask nicotine effects, we administered patches containing 0 (placebo) and 21 mg per day in a second study using the same

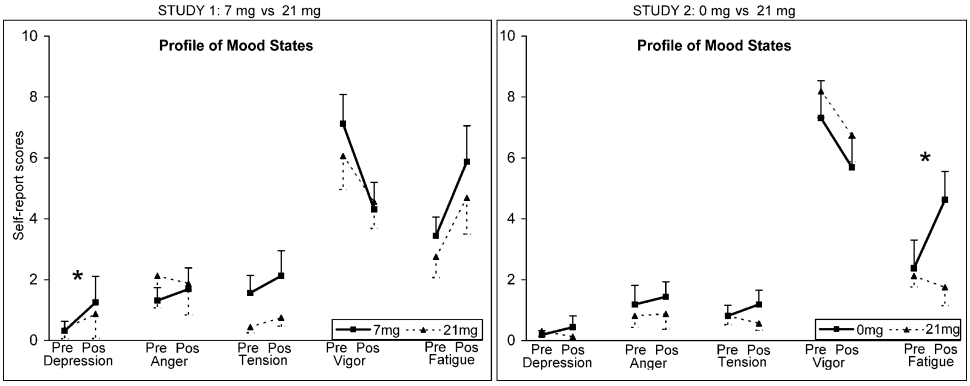

Fig. 3. Mean values for each of the 5 subscales, Depression, Anger, Tension, Vigor and Fatigue (see *x*-axis) of the POMS obtained in Study 1 (left panel) and in Study 2 (right panel), separately for the pre/post measurement. Solid lines correspond to the 7 or 0 mg condition, whereas dotted lines correspond to the 21 mg condition. Bars reflect standard errors. Asterisks indicate significant interaction effects.

design, but a different group of 16 regular smokers. For replication purposes, the reversed CPT (Conners, 1995) and the Profile Of Mood States (POMS) were administered (McNair et al., 1971; Wald and Mellenbergh, 1990). Furthermore, the CPT-AX (Rosvold et al., 1956) and the stop signal task (Logan, 1994), which have traditionally been used to measure response inhibition, were presented.

As for the behavioral measures presumed to reflect attention obtained in Study 1, statistical analysis revealed a trend towards significance (Dose × PrePos) for reaction times in the reversed CPT only. This is in line with the most robust effect reported in previous studies (Levin et al., 1996a,b). In contrast with some previous reports, significant effects were not found for variability of responding and the percentage of omissions (Levin et al., 1998, 2001; White and Levin, 1999). The control study (Study 2) indicated a decrease in reaction times for each of the tasks, and a decrease in variability of responding for the reversed CPT and the stop signal task. Furthermore, in the stop signal task, the percentage of omission was found to increase in the 0 mg condition, but to decrease in the 21 mg condition. Since patterns were similar, but non-significant when comparing the 7 mg and 21 mg condition, we suggest that the use of a low dose as a baseline masked nicotine effects in Study 1, and conclude that nicotine robustly improves attention.

As for behavioral measures presumed to reflect response inhibition obtained in Study 1, a significant interaction was only found for X-only stimuli (X not preceded by A) in the CPT-AX: the percentage of correct rejections decreased in the 7 mg condition, but increased in the 21 mg condition. Although the same pattern was present, this interaction could not be replicated in Study 2. It should be noted that subjects hardly made any false alarms in the CPT-AX, suggesting that ceiling effects might have confounded the statistical analysis of this dependent measure. Furthermore, up until now, we have claimed that false alarms to the X-only reflect response inhibition. This was based on the assumption that the letter X is strongly associated with a go response, which should be inhibited when it is not preceded by a cue (Roberts et al., 1994). However, inattention to the cue could equally well be assumed to underlie incorrect responses to the letter X. Consistent with this notion, rather than interpreting X-only errors in terms of impulsivity, Halperin et al. (1988, 1991) claimed that slow X-only errors reflect inattention, whereas fast X-only errors reflect dyscontrol. In line with this categorization, we conclude that, if anything, the effect on the percentage of correct rejections to X-only stimuli in Study 1 reflects improved attention rather than response inhibition.

In Study 2, a marginally significant interaction was further found for the percentage of correct rejections in the reversed CPT, indicating a larger decrease in the 21 mg condition as opposed to the placebo condition. A similar, but non-significant pattern was found in Study 1. This effect need not reflect deficient response inhibition, given the parallel increase in speed of responding under nicotine. Especially in the reversed CPT, which was designed to enhance subjects' response tendency and thereby increase false alarm rates, the inhibition system may be unable to overcome the increase in response speed, resulting in higher false alarm rates after nicotine administration. Thus, although a decrease in the percentage of correct rejections is usually interpreted in terms of deficient response inhibition, its co-occurrence with faster (and less variable) responses suggests that it merely reflects a side effect of improved attention (to the more frequent go stimuli).

Although findings of improved response inhibition after nicotine administration have been scarce, some previous studies reported (slight) decreases in false alarm rates in non-smokers (Levin et al., 1998). With a group of moderate smokers diagnosed with schizophrenia, an increase in false alarm rates was found with 7 mg patches, whereas a strong decrease in false alarm rates was found with 21 mg patches (Levin et al., 1996b, cited in Riccio et al., 2001). Zack et al. (2001) found that false alarm rates increased in light smokers (<11 cigarettes per day), but decreased in heavy smokers and a decrease in heavy smokers after smoking. Furthermore, various studies indicated deteriorated inhibitory control (increased false alarm rates) after nicotine deprivation (Fried and Watkinson, 1988; Hatsukami et al., 1989; Powell et al., 2002). Importantly, a recent study, in which nicotine (NICODERM, 7 mg per day), methylphenidate and placebo were administered to non-smoking adolescents with ADHD, has reported acute effects of nicotine on SSRT (Potter and Newhouse, 2004). Subjects were selected on the base of displaying SSRTs that were a least

1.5 standard deviations from the mean of normal adolescents (mean value was 305 ms). Nicotine and methylphenidate both produced faster SSRTs than placebo, but had no effect on RT or accuracy. No effects on mood as assessed with the POMS were found. This study suggests that the present absence of nicotine-induced effects on SSRT might be due to ceiling effects in our healthy subjects, especially since the adolescents with ADHD were specifically selected on the base of relatively long SSRTs. Alternatively, these results might indicate that nicotine induced effects on SSRT are more apparent in non-smoking subjects, not characterized by alterations in cholinergic receptors caused by chronic nicotine abuse, but suffering from ADHD.

As for subjective mood states, results were mixed. Study 1 indicated that increases in self-report measures of Depression were smaller in the 21 mg condition than in the 7 mg condition. Previously, the intake of nicotine has been associated with increased feelings of happiness (Warburton and Mancuso, 1998; Levin et al., 2001). Apparently, especially in the 21 mg conditions, euphoric effects of nicotine compensated for feelings of depression, which might have been caused by the relatively long stay in the laboratory. However, this effect could not be replicated in Study 2. This inconsistency might be due to floor-effects, since self-report Depression started off low in the pre treatment session. Consistent with earlier findings (e.g., Gentry et al., 2000), Study 2 indicated that feelings of Fatigue increased under placebo, but decreased after administration of 21 mg nicotine. Previous findings of increased Vigor (Levin et al., 1998, 1996a; Gilbert et al., 2000) and calming effects (Warburton and Mancuso, 1998) could not be replicated. Differences in subjective effects across studies might be related to differences in factors as past smoking behavior, effective dose, method of nicotine administration, or the particular brand of transdermal patches used (Waters and Sutton, 2000; Kalman, 2002).

Taken together, the results suggest that acute nicotine effects are more pronounced for measures presumed to reflect attention than for those presumed to reflect response inhibition. Before actually rejecting the inhibition-hypothesis, some limitations of the present study are noted. First, due to the relatively low number of subjects, insufficient power might underlie the absence of more subtle nicotine effects (on response inhibition). Second, inter-individual differences in effective dose might have increased error variance obscuring small effects on inhibition-related measures. Just as in smoking, plasma concentrations of nicotine vary widely across subjects during transdermal nicotine administration (Gourlay and Benowitz, 1997). Furthermore, differences in body weight, gender, absorption rate and plasma clearance might contribute to error variances that mask nicotine effects. Third, since transdermal patches deliver nicotine in a steadily increasing manner, acute tolerance might have caused the absence of expected effects in Study 1. However, the results of Study 2 as well as previous effects on attentional processing, memory and mood found after 6 h of patch application do not support this notion (Warburton and Mancuso, 1998).

Finally, it should be noted that in Study 1, the 7 mg condition was used as a baseline for the 21 mg condition to avoid confounds related to withdrawal relief. This procedure might have masked genuine effects of nicotine, especially when performance improves in both conditions. Furthermore, the differences between the 7 and 21 mg dose might have been too low to yield significant interaction effects (previous results on dose-related effects of nicotine on cognitive measures are mixed: some studies indicated linear relationships (West and Jarvis, 1986; Jones et al., 1992) or curvilinear relationships (Williams, 1980; Parrott and Craig, 1992), whereas others reported no dose-related effects (Parrott and Winder, 1989; Hindmarch et al., 1990; Mancuso et al., 1999a)). Therefore, we performed a second study in which the 21 mg condition was compared to placebo. The direct comparison of dose conditions in Study 2 might merely reveal effects of withdrawal relief. However, our conclusions are drawn by combining the results of Study 1 and Study 2. Furthermore, the FNDT indicated low dependency ratings in both studies, suggesting relatively mild withdrawal symptoms.

In summary, we conclude that acute nicotine effects are apparent for attention-related measures, but are weak for inhibition-related measures that furthermore might alternatively be interpreted as reflecting improved attention (for the above reasons). Future research should replicate these results in a sample of non-smokers. However, since a sample of non-smokers might not be representative for chronically smoking patients, claimed to use nicotine as a form of self medication, outcomes should be compared to results from a sample of smokers, preferably participating in the same study.

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