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Effects of Nicotine on Response Inhibition and Interference Control

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Abstract

Nicotine is a cholinergic agonist with known pro-cognitive effects in the domains of alerting and orienting attention. However, its effects on attentional top-down functions such as response inhibition and interference control are less well characterised. Here, we investigated the effects of 7mg transdermal nicotine on performance on a battery of response inhibition and interference control tasks. A sample of N=44 healthy adult non-smokers performed antisaccade, stop-signal, Stroop, go/no-go, flanker, shape matching and Simon tasks, as well as the attentional network test (ANT) and a continuous performance task (CPT). Nicotine was administered in a within-subjects, double-blind, placebo-controlled design, with order of drug administration counter-balanced. Relative to placebo, nicotine led to significantly shorter reaction times on a prosaccade task and on CPT hits, but did not significantly improve inhibitory or interference control performance on any task. Instead, nicotine had a negative influence in increasing the interference effect on the Simon task. Nicotine did not alter inter-individual associations between reaction times on congruent trials and error rates on incongruent trials on any task. Finally, there were effects involving order of drug administration, suggesting practice effects but also beneficial nicotine effects when the compound was administered first. Overall, our findings support previous studies showing positive effects of nicotine on basic attentional functions, but do not provide direct evidence for an improvement of top-down cognitive control through acute administration of nicotine at this dose in healthy non-smokers.

Keywords

Nicotine; acetylcholine; cognition; executive function; inhibitory control; attention

Introduction

Nicotine is an agonist at the nicotinic acetylcholine receptor (nAChR) that is widely consumed via smoking of tobacco. Nicotine has been subject to considerable investigation, not only due to its addictive potential but also as it is known to have pro-cognitive effects (Heishman et al. 2010; Newhouse et al. 2011). Studying the effects of nicotine is important not only to provide a fuller understanding of the neurotransmitter systems supporting different aspects of cognition in the healthy brain, but also to improve therapies of nicotine dependence and to develop treatments of cognitive deficits in psychiatric and neurological disorders (Kumari and Postma 2005; Potter et al. 2006).

A recent meta-analysis of healthy non-smokers and minimally withdrawn smokers found that nicotine has positive effects in the domains of attention, fine motor control and memory (Heishman et al. 2010). Effect sizes (Hedges' g) for the alerting and orienting components of attention ranged from .13 to .34. However, in addition to alerting and orienting, attention also serves executive functions (Posner and Petersen 1990; Fan et al. 2002). Executive attention is a top-down cognitive control mechanism whose functions include the suppression of unwanted, bottom-up responses to irrelevant stimuli or stimulus features and the inhibition of the processing of interfering distractors.

Of note, this top-down aspect of attention was not included in the aforementioned meta-analysis as not enough data were available (Heishman et al. 2010). However, such studies are important for a number of reasons. First, executive attentional processes play a prominent role in numerous laboratory tasks and in everyday functioning (Miyake et al. 2000; Miyake and Friedman 2012). Second, impairments in these functions are observed in a number of psychiatric and neurological conditions such as schizophrenia (Barch et al. 2009), ADHD (Barkley 1997) and Alzheimer's disease (Kaufman et al. 2010). Therefore, it is important to better understand the neurotransmitter systems underlying executive attentional processes.

The aim of this study was to investigate effects of nicotine on a battery of inhibition and interference control tasks that pit top-down against bottom-up processing. The tasks were chosen in order to tap two important and related facets of inhibitory control that were defined on the basis of the work by Friedman and Miyake (2004), namely "*prepotent response inhibition*" and "*resistance to distractor interference*" (Friedman and Miyake 2004). Prepotent response inhibition refers to the ability to withhold a normally appropriate motor, oculomotor or verbal response to a stimulus when inappropriate within a specific context. Resistance to distractor interference, or interference control, refers to the ability to "resist or resolve interference from information in the external environment that is irrelevant to the task at hand" (Friedman and Miyake 2004). Whilst this distinction has received empirical support (Friedman and Miyake 2004), it should be noted that "inhibition" is a heterogeneous concept and that the term may comprise many more functions. Accordingly, other taxonomies of this construct have also been proposed (for a comprehensive overview, see Bari and Robbins 2013).

Following Friedman and Miyake (2004) and incorporating conceptually related inhibition and interference control tasks, we put together the following test battery: To assess response inhibition, we chose the antisaccade, stop-signal, Stroop and go/no-go tasks. To assess interference control, we selected the flanker, shape matching and Simon tasks. Additionally, we included the Attention Network Test (ANT; Fan et al. 2005) and the identical pairs version of the

continuous performance task (CPT; Cornblatt et al. 1988). The ANT measures alerting, orienting and executive aspects of attention. The CPT is not only a sustained attention task but also provides an indicator of response inhibition, viz. the rate of commission errors on catch trials.

The selected response inhibition and interference control tasks share prefrontal cognitive control mechanisms that flexibly bias information processing and responding towards task goals, and away from competing, but irrelevant, information and inappropriate responses (Miller and Cohen 2001). Theoretical accounts explain performance on these and related tasks in terms of the competition between a dominant, largely automatic bottom-up processing stream and a weak, top-down processing stream requiring top-down control (Dunbar and MacLeod 1984; Miller and Cohen 2001; Hutton and Ettinger 2006).

These models have implications for the study of nicotine effects: Stimulation of acetylcholine receptors may enhance attentional bottom-up processing of stimuli, top-down cognitive control processes biasing stimulus-response transformations or both. Given the paucity of nicotine studies on executive attention (Heishman et al. 2010), it remains an empirical question to carefully characterise the compound's effects on inhibition and interference control tasks within the framework of bottom-up / top-down competition models. Whilst previous evidence has mostly pointed to positive effects on more basic attentional functions such as orienting and simple visuo-motor transformations (Heishman et al. 2010), there are also reports of beneficial effects on top-down control (AhnAllen et al. 2008; Wignall and De Wit 2011; for review, see Ettinger and Kumari 2003; Reilly et al. 2008). Crucially, within the framework of competition models, facilitatory effects of nicotine on bottom-up processes may counteract implementation of top-down control in trials with weak stimulus-response mappings. On the other hand, it has been argued that nicotine exerts general stimulant effects on arousal without specific influences on selective attention (Provost and Woodward 1991), which would predict improved performance on both bottom-up and top-down processes.

Previous studies have provided mixed evidence of nicotine effects on response inhibition in healthy humans. There is evidence of nicotine effects on antisaccade error rates and latencies (Ettinger and Kumari 2003; Hutton and Ettinger 2006; Reilly et al. 2008), but findings on the stop-signal task are less consistent (Bekker et al. 2005; Wignall and De Wit 2011; Potter et al. 2012). Regarding Stroop, nicotine has been found to reduce the interference effect in some (Wignall and De Wit 2011), but not in other studies (Suter et al. 1983; Wesnes and Revell 1984; Foulds et al. 1996; Mancuso et al. 1999; Barr et al. 2008) of healthy volunteers. Positive nicotine effects on Stroop have also been reported in schizophrenia (Barr et al. 2008) and ADHD (Potter and Newhouse 2004), although a later study found *increased* reaction times with nicotine in ADHD (Potter and Newhouse 2008). Commission errors on the go/no-go task appear not to be affected by nicotine (Giessing et al. 2013; Smucny et al. 2015), but two studies found higher error rates in smokers than non-smokers (Dinur-Klein et al. 2014; Yin et al. 2015), suggesting that long-term nicotine administration may have detrimental effects on prepotent response inhibition.

Regarding interference control, one study reported more efficient executive control with a nicotine patch in the ANT (AhnAllen et al. 2008). Another study observed an overall reduction in reaction time and an improvement in correct

response rate in smokers following oral snuff (Lindgren et al. 1996), but there are also failures to observe nicotine effects on the flanker task (Lindgren et al. 1996; Kleykamp et al. 2005; Wignall and De Wit 2011; Myers et al. 2013). Additionally, a study of the non-competitive nicotinic receptor antagonist mecamylamine observed neural effects during the executive condition of the ANT (Thienel et al. 2009) and two studies observed post-error processing abnormalities in flanker tasks in smokers compared to non-smokers (Franken et al. 2010; Luijten et al. 2011), suggesting long-term effects of nicotine. In a study of a modified Simon task, nicotine-deprived smokers responded more slowly than non-deprived smokers (Schlam et al. 2011), but we are not aware of any studies of the effects of nicotine administration on the Simon effect. Similarly, we did not find any studies of nicotine effects on the shape matching task (DeSchepper and Treisman 1996; Miyake et al. 2000), which would be important to estimate effects of nicotine on interference control.

Overall, the evidence base regarding nicotine effects on inhibition and interference control is thus somewhat inconsistent and in need of further studies. Here, we aimed to contribute towards addressing this important issue. We wished to provide a fine-grained assessment of the effects of nicotine on a range of conceptually overlapping tasks that tap the competition between dominant and weak processing streams. In order to circumvent the known problems of studying nicotine effects in smokers, our study included only non-smokers. In order to achieve sufficient sensitivity to nicotine effects we recruited a sample size considerably larger than the average sample size of studies in the meta-analysis by Heishman et al. (2010). Moreover, given previous evidence of the baseline dependency of pro-cognitive pharmacological effects (Mehta 2002), we considered the role of baseline performance in nicotine effects.

We also aimed to extend our investigation beyond nicotine effects on average performance measures by considering correlations amongst dependent variables. Previous studies have reported negative correlations between reaction times on trials that can be resolved using the dominant response and error rates on trials in which the dominant response must be suppressed (Ettinger et al. 2005; Pierce and McDowell 2016; Talanow et al. 2016), although not all have found this (Giessing et al. 2013)[1]. This correlation, essentially reflecting an inter-individual speed-accuracy trade-off, can be predicted from the theoretical foundations of competition accounts (Massen 2004; Noorani and Carpenter 2013). Therefore, we also investigated whether nicotine affected these correlations, which might provide evidence of inter-individual response variability in one or both of the components of the competition (Ettinger et al. 2009).

On the basis of previous evidence of nicotine effects on alerting and orienting attention (Heishman et al. 2010), we hypothesised that the substance would improve bottom-up attentional processes and we explored effects on top-down control as well as the relationships between measures of bottom-up and top-down processes.

Method

[1] Further support comes from a re-analysis of our previously published data (Polner et al. 2015) from a sample of N=440: There were significant correlations between congruent RT and incongruent/no-go error rate for the saccade ($r=-.25$, $p<.001$), flanker ($r=-.18$, $p<.001$) and go/no-go ($r=-.46$, $p<.001$) but not the Simon task ($r=.05$, $p=.22$). Stroop data from that study were not available on an individual trial level and were thus not included in this re-analysis.

Sample

Healthy non-smoking volunteers were recruited via flyers, an online job board of the University of Bonn and via e-mails to different faculties of universities in Bonn and Cologne. Potential participants were invited to a telephone screening in which exclusion criteria were addressed. Participants were screened for any past or present psychiatric diagnoses (Lecrubier et al. 1997), cardiovascular diseases, high blood pressure, inflammatory skin diseases, liver and kidney dysfunctions, stomach or intestinal ulcers, hyperthyroidism, adrenal tumour, insulin-dependent diabetes, internal diseases, diseases of the central nervous system, drug and alcohol abuse, pregnancy, a body mass index (BMI) <18.5 and weight <50kg. Other requirements were that participants were between 18 and 45 years old, had smoked less than five cigarettes in their entire life and were not on regular medication. Females were required to be taking oral contraceptives to ensure a constant hormone level.

The study was approved by the ethics committee of the Department of Psychology, University of Bonn, and participants provided written informed consent. Participants were compensated with either course credits or €50.

Design and Procedure

The study involved a baseline session followed by a two-session, within-subject, double-blind, placebo-controlled design comparing effects of a 7mg transdermal nicotine patch (NiQuitin Clear 7mg, GlaxoSmithKline Consumer Healthcare GmbH & Co. KG, Bühl, Germany; PZN -2919658) with a placebo patch of similar appearance (Rheumaplast, Beiersdorf AG, Hamburg, Germany; PZN -4010194). Both patches were applied to the participant's upper back by a research assistant who was not running the test sessions and without the participants seeing the patch, in order to ensure double blindness. The order of the experimental conditions (drug or placebo), as well as the cognitive tasks, was randomized across participants.

In the baseline session, participants were informed of the study details and provided written consent. They completed several questionnaires (see below) and practised the cognitive tasks that were presented in the two following study sessions. Additionally, participants were selected randomly to undergo a drug urine test (Drug-Screen Multi 5T, nal von minden GmbH, Regensburg, Germany).

In both study sessions, participants completed a battery of cognitive tasks beginning three hours after application of the patch. This time point was chosen on the basis of evidence that nicotine plasma levels reach a plateau within 2-4 hours after transdermal application (Gorsline et al. 1992). A previous study using a 7mg transdermal patch showed that nicotine plasma levels (Cmax) were on average 8.3ng/ml (SD=1.9) (Gorsline et al. 1993). Before patch application as well as before and after cognitive task performance, participants also filled in computerised visual analogue scales (VAS; Norris 1971). The duration of the cognitive battery was 50-60 minutes. Each study session was conducted between 8am and 8pm, with time of assessment controlled for each participant (Table 1). With few exceptions, the two study sessions were separated by seven days. At the end of each study session, participants were asked to guess which patch they had received (forced choice: nicotine or placebo).

Participants were told not to drink any alcohol the day before assessments and they had to abstain from eating and drinking except for water during the study sessions.

Demographic and Intelligence Assessment

Age (in years) and gender (male/female) were measured using a demographics questionnaire. Handedness was assessed (Oldfield 1971) and a measure of verbal IQ was obtained (MWT-B; Lehrl et al. 1995). The MWT-B is a widely used German measure of verbal ability and requires the identification of a word amongst four non-word distractors in each of 37 trials.

Visual Analogue Scales

During each of the two study sessions, participants indicated their current mood state by moving a cursor along VAS presented on a computer screen for each of 16 items, following the method of Norris (1971). Ratings were obtained before patch administration, before beginning the cognitive tasks and after completing the cognitive tasks. The items were later averaged into the factors mental sedation, physical sedation, tranquilisation and other feelings following Norris (1971). Higher factor scores indicate more negative mood states for mental sedation, physical sedation and other feelings (with the latter including the items sad, antagonised, bored and withdrawn). For tranquilisation, higher scores indicated more positive feelings (calm, contented, tranquil and relaxed).

Cognitive Tasks

Flow charts of all tasks are provided in Supplementary Figures 1-9.

The *saccade task* included prosaccades and antisaccades and was written using the SR Research ExperimentBuilder software (SR Research Ltd., Ottawa, Ontario, Canada) and displayed using a 19-inch monitor. Participants' head movements were minimized by the use of a chin rest with a distance from eye to screen of 70cm. Before the task, the eye-tracker was calibrated with a horizontal 3-point calibration task. Each trial required participants first to look at a yellow (RGB: 255,255,0) or blue (0,0,255) central fixation cue, which was presented on black (0,0,0) background for a random duration of 1000–2000ms. The target, a white (255,255,255) circle, was then immediately presented on the same background for 1000ms, randomly at one of four possible horizontal positions (±7.25°; ±14.5° from the fixation point). Each of the peripheral locations was used 15 times in a total of 60 trials. Dependent of the colour of the central fixation cue, participants were instructed to perform a horizontal saccade towards the peripheral target (prosaccade) or to the opposite position of the target (antisaccade), with colour-instruction mapping counterbalanced across participants. In 50% of the trials, the target appeared on the right side of the screen, in 50% it appeared on the left side. The task comprised 30 prosaccade and 30 antisaccade trials, presented in random order.

Movements of the dominant eye were recorded using a combined corneal reflection and pupil tracker (EyeLink 1000, SR Research Ltd.) at a sampling frequency of 1000 Hz. Saccades were identified using the DataViewer software (SR Research Ltd.). Criteria for the identification of saccades were a minimum amplitude of 1° and a minimum latency to target of 80ms. The dependent variables were the percentage of directional errors and mean latencies of directionally correct saccades (the time between the onset of the target and the onset of the saccade in ms).

The *stop-signal task* (Rubia et al. 2007) was run on a 19-inch monitor at a distance of approximately 80cm from participants. In a go-trial, a white (RGB: 255,255,255) arrow pointing left or right on black (0,0,0) background was presented for 1000ms followed by a black screen lasting for 700ms. In stop trials (27% of all trials) the presentation of the arrow was followed by the appearance of the stop-signal – a white arrow pointing up – which appeared initially 250ms after the onset of the go-signal and lasted 300ms. Participants were instructed to press an arrow key corresponding to the stimulus (right or left) or to stop their ongoing response if the stop-signal appeared. The task consisted of 178 trials. There were 130 go-trials (with 50% of each direction) and 48 stop-trials (with 50% of stop-signals appearing either after a left- or after a right-pointing arrow). The task included a tracking procedure, which ensured that participants successfully inhibited on approximately 50% of the stop-signal trials by dynamically adjusting the interval between the go- and the stop-signal (Rubia et al. 2007). The dependent variables were the stop signal reaction time (SSRT), calculated in ms by subtracting stop-signal delay from mean go reaction time, and the mean reaction times (ms) of correct go and incorrect stop trials.

The *Stroop task* was written in Presentation (Neurobehavioral Systems, Inc., Berkeley, CA, USA) and presented using a 19-inch monitor. Participants were seated from the monitor at a distance of approximately 80cm. The screen background was set to grey (RGB: 150,150,150). Each trial began with a black (0,0,0) central fixation cross for 300ms, followed by the target stimulus, which consisted of a colour word or horizontal bar that was shown in the centre of the screen until response. Target stimuli were shown in red (255,0,0), yellow (255,255,0), green (0,255,0) or blue (0,0,255). Participants were instructed to respond to the colour in which the words (the German words “ROT” (red), “GELB” (yellow), “GRÜN” (green), or “BLAU” (blue)) or the bars were presented by pressing a corresponding key (the C, V, N and M keys on a QWERTZ keyboard were marked with colour stickers). In the incongruent condition, the colour words and word colour did not match, whereas in the congruent condition they matched. The colour bars represented the neutral condition. The task consisted of 144 trials, with 48 trials for each condition, presented in random order. In the congruent and the colour bar conditions, there were 12 trials for each colour, while in the incongruent condition, there were 4 trials for each combination of colours. Dependent variables were the mean reaction times (ms) of correct responses and the percentage of errors for each condition.

The *go/no-go task* was written in Presentation and presented using a 19-inch monitor. Participants were seated from the monitor at a distance of approximately 80cm. The task consisted of 110 go-trials and 40 no-go-trials presented in random order. Participants were instructed to respond by pressing the space bar when the go-stimulus (a grey circle; RGB: 115,115,115) was shown but to withhold a response when the no-go-stimulus (a blue circle of identical size; 0,0,255) was presented. The stimuli were presented in the centre of a black (0,0,0) screen for 500ms, followed by a black screen lasting for 700ms. The dependent variables were the percentage of errors on no-go trials (so-called commission errors) as well as the mean reaction times (ms) of correct go and incorrect no-go trials.

The *flanker task* was written in Presentation and presented using a 19-inch monitor. Participants were seated from the monitor at a distance of approximately 80cm. The screen background was set to black (RGB: 0,0,0). Participants were instructed to respond to a central arrow in an array of five horizontally aligned, white (255,255,255) arrow

shapes. The target was either a ">" or a "<" and participants had to respond with one of two corresponding keys. The flankers were incongruent (e.g. ">><>>"), congruent (e.g. "<<<<<") or neutral (e.g. "□□>□□"). There were 50 trials in each condition (incongruent, congruent, neutral), presented in random order. Each trial began with a central fixation cross for 500ms. The stimulus array was then presented for 1000ms, followed by a black screen of 1000ms. The dependent variables were the mean reaction times (ms) of correct responses and error percentages for each condition.

The *shape matching task* (DeSchepper and Treisman 1996) was written in Presentation and presented using a 19-inch monitor. Participants were seated from the monitor at a distance of approximately 80cm. In each trial, a green (RGB: 0,255,0) and a white (255,255,255) figure were presented at the left and the right sides of the computer screen. Participants had to decide whether these figures were identical in shape or not by pressing the left or right arrow keys on the keyboard, respectively. In some of the trials, the green figure was overlaid by a red (255,0,0) figure, which was irrelevant for the task and served as a distractor. There were four Task Conditions: There was no distractor and the green and the white figures were identical (no distractor – same); there was a distractor and the green and the white figures were identical (with distractor – same); there was no distractor and the two figures were not identical (no distractor – different); and there was a distractor and the two figures were not identical (with distractor – different). Twenty trials were presented in each condition in a random order. Trials began with a central fixation cross for 600ms, followed by the stimuli which were presented until response. Immediately following the response, the stimuli on both sides were replaced by a 100ms visual noise mask. Trials were separated by a 1000ms blank screen. The dependent variables were the mean reaction times (ms) of correct responses and error percentages for each condition.

The *Simon task* was written in Presentation and presented using a 19-inch monitor. Participants were seated from the monitor at a distance of approximately 80cm. The task was modified from the paradigm developed by Simon and Small (Simon and Small 1969). The screen background was set to black (RGB: 0,0,0). Each trial consisted of a white (255,255,255) central fixation cross, presented for 1100ms, followed by a white arrow shape, presented for 400ms. Arrow shapes pointed to the right or to the left and were presented on the right or left side of the screen. Participants were instructed to indicate the direction of the arrows whilst ignoring their position by pressing a corresponding arrow key on the keyboard. In a congruent trial, direction and position of the arrow were identical. In an incongruent trial, direction and position differed (e.g. an arrow pointing right appeared on the left side). For each of the conditions (right congruent, right incongruent, left congruent, left incongruent), 30 trials were presented, resulting in a total of 120 trials presented in random order. The dependent variables were the mean reaction times (ms) of correct responses and error percentages for each condition.

The *Attention Network Test (ANT)* (Fan et al. 2005) was presented via E-Prime (Psychology Software Tools, Inc., Sharpsburg, PA, USA). Stimuli were displayed on a 19-inch monitor at a viewing distance of approximately 80cm. Stimuli consisted of a row of five horizontal black arrows, the target being the central arrow, flanked on either side by two arrows in the same direction (congruent condition), or in the opposite direction (incongruent condition). The participants' task was to indicate the direction of the target arrow by pressing the corresponding mouse button (i.e. the left mouse button for a leftward arrow and the right mouse button for a rightward arrow). A trial began with a

fixation cross (random duration 400-1600ms), followed by a 100ms cue period. In this cue period, either no cue (100ms fixation cross), a central cue (i.e. a central asterisk), or a valid spatial cue (i.e. flashing at the corresponding target location) was presented. A 400ms fixation period followed, and subsequently, targets and flankers appeared simultaneously until the participant responded or until 1700ms elapsed. A post-target fixation period followed based on the initial fixation time and reaction time of the participant so that each trial lasted for 4000ms. There were 96 trials (i.e. two blocks of 48 trials). One block included 16 no cue trials, 16 central cue trials, and 16 spatial cue (8 up, 8 down) trials. Dependent variables were the alerting, orienting and conflict effect scores, calculated by subtracting RTs of centre cue from no cue trials (alerting), spatial cue from centre cue trials (orienting) and congruent from incongruent trials (conflict).

The *continuous performance task (CPT)* based on Cornblatt's identical pairs version (Cornblatt et al. 1988) was written in Presentation and presented using a 19-inch monitor. Participants were seated from the monitor at a distance of approximately 80cm. Stimuli were numbers made up of four digits, presented in white (RGB: 255,255,255) on black (0,0,0) background. Each stimulus was presented for 50ms, followed by a black screen for 950ms. Participants were required to press the space bar as quickly as possible when a number was presented except when an "identical pair" was presented, i.e. when there was an exact repetition of numbers (e.g. 9004-9004). There were also catch trials, consisting of pairs of stimuli were one of the two middle digits had been exchanged (e.g. 8617-8657). The remaining stimuli were singletons, not resembling a previous or following stimulus, randomly interleaved amongst pairs and catch pairs. The dependent variables were the percentage of false alarms (responses to the second, identical stimulus in a pair) as well as the mean reaction time (ms) of hits.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 22.0 (IBM, Armonk, NY, USA).

First, for the saccade, Stroop, shape matching and Simon tasks, data from a number of participants were excluded from all variables of a given session when it appeared that they had failed to adhere to instructions, which could be told by high error rates as described in the following: Two participants with an antisaccade error rate of 100% were excluded from the saccade task for all sessions. For the stop-signal task, several participants were excluded from the whole task because of a negative SSRT (seven participants) or a very low (<10%) or very high (>80%) rate of inhibition trials (two participants). For the Stroop task, one participant with 44 errors out of 48 trials in the incongruent condition was excluded for all sessions. In the shape matching task, three participants with 16 or more errors (out of 20 trials) in the placebo and/or the nicotine measure were excluded. One participant was excluded from the Simon task during nicotine due to failure to complete any of the congruent trials correctly. In addition, due to measurement complications, data were missing for the stop-signal task for two participants.

Second, all dependent variables were tested for normality of distribution in the different placebo and nicotine conditions. Normal distribution was assumed when skewness was between -1 and +1 for at least two of the three conditions and only slightly below or above for the third condition. Otherwise, variables were transformed using log transformation.

Next, inferential statistical analyses were carried out with significance set at $p<0.05$. Each VAS factor was analysed using analysis of variance (ANOVA) with the within-subjects factors Drug (placebo, nicotine) and Time (pre-patch, pre-tasks and post-tasks) and the between-subjects factor Order (Plc-Nic, Nic-Plc).

Each cognitive task was analysed separately using ANOVA. For each task, the ANOVA comprised the within-subjects factor Drug (placebo, nicotine) and the between-subjects factor Order (Plc-Nic, Nic-Plc) as well as task-related factors described individually below. A within-subjects factor Task Condition was added for the saccade task (prosaccades, antisaccades), for the Stroop task (incongruent, congruent, colour bar), for the flanker task (incongruent, congruent, neutral) and for the Simon task (incongruent, congruent). For the mean reaction times (MRT) in the stop-signal and go/no-go tasks, the factor Response Type (correct response to go trials, incorrect response to stop trials) was included in the analyses. The shape matching task had two further within-subjects factors: Task Condition (same, different) and Distractor (with distractor, without distractor). For other tasks and dependent variables, Drug and Order were the only two factors. Significant interactions were followed up with t-tests.

Additionally, given that it has previously been shown that the magnitude and direction of nicotine effects may depend on baseline performance, we searched for baseline dependency effects in each dependent variable. This was done by splitting the sample into high and low performers on the basis of their baseline performance data. ANOVA models were then carried out for each variable comprising the within-subjects factor Drug (placebo, nicotine) and the between-subjects factors Order (Plc-Nic, Nic-Plc) and Baseline (low, high).

Pearson correlations were carried out, separately for the nicotine and placebo conditions, between cognitive variables and VAS ratings obtained just before cognitive testing began.

Pearson correlations were also carried out for pairs of variables indexing, for each task, the MRT on dominant trials (prosaccade latency; Stroop congruent MRT; go/no-go task go MRT; flanker MRT of neutral trials; shape matching MRT of trials without distractors (same); Simon MRT of congruent trials; continuous performance task MRT of hits) and the error rate on non-dominant trials (antisaccade direction errors; Stroop incongruent errors; go/no-go task no-go errors of commission; flanker task error rate on incongruent trials; shape matching error rate on trials with distractors (same); Simon error rate of incongruent trials; continuous performance task false alarm rate). These were expected to be negative and their magnitudes were compared between the nicotine and placebo sessions using a version of the Pearson-Filon test statistic that employs a Fisher's z transformation of the Pearson correlation coefficient (ZPF; Raghunathan et al. 1996).

Results

Sample Description

A total of 51 participants took part. Seven participants were excluded from analysis, as they dropped out of the study after the first or the second session. The final sample thus consisted of 44 participants (17 males, 27 females) (Table

1). Twenty-three participants received nicotine first, 21 received placebo first. The two order groups did not differ in age, gender, IQ, handedness, time interval (in days) between first and second study session or time difference (in minutes) between time point of patch application at first and second assessment (all p>.13). Participants could not reliably guess at either study session whether they had received placebo or nicotine (both p>.05). Descriptive statistics of VAS are in Table 2. Descriptive statistics of cognitive performance variables are in Table 3.

INSERT TABLES 1-2 ABOUT HERE

Visual Analogue Scales

For mental sedation, there were main effects of Drug ($F_{(1,42)}$=7.47, p=.01, η_p^2=.15) and Time ($F_{(2,84)}$=19.06, p<.001, η_p^2=.31) as well as interactions between Drug and Order ($F_{(1,36)}$=4.09, p=.05, η_p^2=.09) and Time and Order ($F_{(2,84)}$=3.16, p=.047, η_p^2=.07), but no further effects (all p>.20). The effect of time was linear (p<.001), but not quadratic (p=.21). The main effects indicate higher scores (more negative feelings) with nicotine than placebo and increasing scores over time. The interaction between Drug and Order indicates an overall reduction in ratings from first (nicotine) to second (placebo) study session in the Nic-Plc group (p=.01), whereas no significant difference occurred for the Plc-Nic group (p=.47). The interaction between Time and Order stems from a continued increase in ratings from pre- to post-task in the Plc-Nic group, but not the Nic-Plc group. For descriptive statistics, see Table 2. For follow-up t-tests, see Supplementary Tables 1-3.

For physical sedation, there were main effects of Drug ($F_{(1,42)}$=8.83, p=.01, η_p^2=.17) and Time ($F_{(2,84)}$=9.51, p<.001, η_p^2=.19) as well as an interaction between Drug and Time ($F_{(2,84)}$=3.18, p=.046, η_p^2=.07), but no further effects (all p≥.07). The effect of time was linear (p<.001), but not quadratic (p=.24). The main effects indicate higher scores (more negative feelings) with nicotine than placebo and increasing scores over time. The interaction indicated that the increase from pre-patch to pre-task was significant for the nicotine (p=.01) but not the placebo (p=.43) condition. In addition, there was a significant increase from pre- to post-task in the placebo (p=.01) but not the nicotine (p=.79) condition. For descriptive statistics see Table 2. For follow-up t-tests see supplementary materials.

For tranquilisation, there was a main effect of Drug ($F_{(1,42)}$=6.27, p=.02, η_p^2=.13), indicating lower scores (more negative feelings) with nicotine than with placebo, but no other effects (all p>.21). For descriptive statistics see Table 2.

For other feelings, there were main effects of Drug ($F_{(1,42)}$=4.63, p=.04, η_p^2=.10), indicating higher scores (more negative feelings) with nicotine than with placebo, and Time ($F_{(2,84)}$=9.29, p<.001, η_p^2=.18), indicating increasing scores over time, but no other effects (all p>.11). The effect of time was linear (p<.001), but not quadratic (p=.31). For descriptive statistics see Table 2.

INSERT TABLES 3-4 AND FIGURES 1-6 ABOUT HERE

Saccade Task

The ANOVA for latency found a main effect of Task Condition, indicating shorter latencies for prosaccades than for antisaccades ($F_{(1,36)}$=158.81, p<.001, η_p^2=.82), but no main effect of Drug (p=.39). There was an interaction between Drug and Task Condition ($F_{(1,36)}$=5.48, p=.03, η_p^2=.13), indicating shorter mean latencies with nicotine compared to placebo for prosaccades ($t_{(41)}$=2.23, p=.02), but not for antisaccades (p>.32) (Fig. 1). For both Drug conditions, t-tests revealed significant differences between the latencies of prosaccades and antisaccades ($t_{(40)}$=12.55, p<.001 for placebo; $t_{(40)}$=14.09, p<.001 for nicotine).

A main effect of Task Condition also occurred for error rate, indicating fewer errors for prosaccade than antisaccade trials ($F_{(1,37)}$=93.57, p<.001, η_p^2=.72). No main effect of Drug was found (p=.48), but there was an interaction between Order, Drug and Task Condition ($F_{(1,37)}$=5.88, p=.02, η_p^2=.14) (Fig. 1). In both Order groups, fewer prosaccade errors occurred in the second compared to the first study session. However, post-hoc t-tests indicated that this difference was significant only for the Nic-Plc group ($t_{(21)}$=-1.87, p=.038), but not for the Plc-Nic group (p>.08). In contrast, both Order groups made fewer antisaccade errors during nicotine than placebo; however, these differences did not reach significance (both p>.11). Finally, post-hoc t-tests indicated more errors during antisaccades than prosaccades in both groups for both nicotine and placebo (all p<.001).

Correlations of prosaccade latency with antisaccade direction errors were not significant for either nicotine or placebo (Table 4). The comparison of correlations between the nicotine and placebo conditions was also not significant (p=.55).

Stop-Signal Task

For SSRT, there were no main or interaction effects (all p>.32).

For MRTs, a main effect of Response Type was found ($F_{(1,37)}$=10.23, p=.003, η_p^2=.22), indicating shorter MRTs for incorrect responses to stop trials compared to MRTs for correct responses to go trials. There was a main effect of Order ($F_{(1,37)}$=16.84, p<.001, η_p^2=.31), indicating shorter MRTs for the Plc-Nic group, but no other main or interaction effects (all p>.07).

Correlations between go trials MRT and SSRT were not significant for either nicotine or placebo (Table 4). The comparison between the nicotine and placebo conditions was also not significant (p=.67).

Stroop Task

For MRTs of correct responses, a main effect of Task Condition ($F_{(2,82)}$=61.55, p<.001, η_p^2=.60) indicated that MRTs were higher for incongruent trials than for congruent and colour bar trials. There was no main effect of Drug (p=.994) but an interaction between Drug and Order ($F_{(1,41)}$=9.54, p=.004, η_p^2=.19) indicated shorter MRTs in the second than the first study session regardless of the drug condition, suggesting practice effects. T-tests showed that these differences reached significance for both the Nic-Plc group ($t_{(22)}$=-2.04, p=.03) and the Plc-Nic group ($t_{(19)}$=2.46, p=.01). The two order groups differed significantly in their MRTs in the nicotine condition ($t_{(41)}$=2.20, p=.02), but not in the placebo condition (p>.45).

There was also an interaction between Drug, Task Condition and Order ($F_{(2,82)}$=4.17, p=.02, η_p^2=.09) (Fig. 2). This effect indicated that in both order groups, MRTs were shorter in the second study session compared to the first study session, but that the size of this difference depended on Task Condition. According to post-hoc t-tests, within the Nic-Plc group, this difference was significant only for incongruent ($t_{(22)}$=-1.95, p=.03) and congruent ($t_{(22)}$=-2.20, p=.02) trials, but not for colour bar trials (p=.15). For the Plc-Nic group, this difference was significant only for incongruent trials ($t_{(19)}$=3.06, p=.004), but not for congruent and colour bar trials (both p>.05). For the Nic-Plc group, MRTs were shorter for congruent trials and for colour bar trials, compared to incongruent trials, both in the placebo condition ($t_{(22)}$=-4.34, p<.001; $t_{(22)}$=4.72, p<.001) and in the nicotine condition ($t_{(22)}$=-5.75, p<.001; $t_{(22)}$=6.25, p<.001). In the nicotine condition, MRTs for colour bar trials were significantly shorter than MRTs for congruent trials ($t_{(22)}$=1.87, p=.04); in the placebo condition, there was no difference between these two Task Conditions (p=.50). For the Plc-Nic group, this pattern was similar: MRTs were shorter for congruent trials and for colour bar trials, compared to incongruent trials, both in the placebo condition ($t_{(19)}$=-7.21, p<.001; $t_{(19)}$=6.10, p<.001) and in the nicotine condition ($t_{(19)}$=-2.98, p=.004; $t_{(19)}$=3.51, p=.001). For both placebo and nicotine, there were no differences between the MRTs of congruent and colour bar trials (both p>.21).

For error rates, there was no main effect of Drug (p=.91) but an interaction effect between Drug and Order ($F_{(1,41)}$=5.75, p=.02, η_p^2=.12) indicating higher error rates in the second study session than the first one (Fig. 2). T-tests showed significant differences between error rates in the two drug conditions for the Plc-Nic group ($t_{(19)}$=-1.77, p=.047) and, at trend level, for the Nic-Plc group (p=.05). The two order groups did not differ significantly from each other in their error rates, neither in the nicotine, nor in the placebo condition (both p>.18).

Correlations between MRT of congruent trials and error rates on incongruent trials were neither significant for the nicotine nor the placebo conditions (Table 4). The comparison of these correlations between the nicotine and placebo conditions was also not significant (p=.17).

Go/No-go Task

A main effect of Response Type ($F_{(1,26)}$=162.63, p<.001, η_p^2=.86) showed that MRTs for incorrect responses to no-go trials were shorter than MRTs for correct Go trials. There were no main effects of Drug or Order and no interactions involving any factors for MRTs (all p>.18).

For no-go error rate, there were no main effects of Drug or Order and no interaction (all p>.17).

Correlations between go trials MRT and no-go trials error rate were significant for both nicotine and placebo conditions (Table 4). The comparison between these correlations across nicotine and placebo conditions was not significant (p=.99).

Flanker Task

For MRTs of correct responses, a main effect of Task Condition was found ($F_{(1,84)}$=196.96, p<.001, η_p^2=.91). Correct responses to incongruent trials had significantly longer MRTs than responses to congruent and neutral trials. There was no main effect of Drug (p>.87) and no interaction between Drug and Task Condition (p>.87), but an interaction between Drug and Order ($F_{(1,42)}$=7.63, p=.01, η_p^2=.15) indicating that MRTs were shorter in the second than the first study session (Fig. 3). T-tests showed that these differences were significant both for the Nic-Plc group ($t_{(22)}$=-1.89, p=.04) and for the Plc-Nic group ($t_{(20)}$=2.01, p=.03). The two Order groups did not differ significantly, neither in the placebo condition nor in the nicotine condition (both p>.13).

The ANOVA for error rates revealed a non-significant main effect of Drug ($F_{(1,42)}$=3.23, p=.08, η_p^2=.07), suggesting fewer errors with nicotine than with placebo. There was no main effect of Order and no interactions (all p>.12).

Correlations of MRT of neutral trials with error rate on incongruent trials were significant for both nicotine and placebo conditions (Table 4). The comparison between nicotine and placebo conditions for these correlations was not significant (p=.30).

Shape Matching Task

For MRTs of correct responses, a main effect of Distractor ($F_{(1,39)}$= 184.82, p<.001, η_p^2=.83) showed that MRTs were shorter for trials without a distractor. There was no main effect of Drug (p>.56), but an interaction between Drug and Order ($F_{(1,39)}$=8.37, p=.01, η_p^2=.18), indicating that MRTs were shorter in the second compared to the first study session (Fig. 4). T-tests showed that these differences reached significance only for the Nic-Plc group ($t_{(22)}$=-3.04, p=.003), but not for the Plc-Nic group (p>.09). The two order groups did not differ significantly in their MRTs, neither in the placebo condition, nor in the nicotine condition (both p>.13). In addition, an interaction effect between Task Condition and Distractor was found ($F_{(1,39)}$=99.51, p<.001, η_p^2=.72). For trials with a distractor, MRTs were shorter when the stimulus was different ($t_{(40)}$=8.04, p<.001), while for trials without a distractor, MRTs were shorter when the stimulus was the same ($t_{(40)}$=-6.00, p<.001). Furthermore, MRTs were shorter for stimuli without a distractor than for stimuli with a distractor, both for same stimuli ($t_{(40)}$=14.58, p<.001) and for different stimuli ($t_{(40)}$=9.09, p<.001). No other main or interaction effects were significant (all p>.05).

For error rates, a main effect of Distractor ($F_{(1,39)}$=28.90, p<.001, η_p^2=.43) indicated that participants made fewer errors in trials without a distractor. An interaction effect between Task Condition and Distractor ($F_{(1,39)}$=5.33, p=.03, η_p^2=.12) showed that for trials with distractor, fewer errors were made when the stimulus was different, while for trials without distractor it was the other way round. T-tests found a significant difference only for trials without a distractor ($t_{(40)}$=-2.00, p=.03), but not for trials with a distractor (p>.13). Furthermore, fewer errors were made for stimuli without a distractor than for stimuli with a distractor, both for same stimuli ($t_{(40)}$=4.58, p<.001) and for different stimuli ($t_{(40)}$=2.12, p=.02). No other main or interaction effects were significant (all p>.18).

Correlations of MRT of trials without distractors (same) with error rate on trials with distractors (same) were significant for both nicotine and placebo conditions (Table 4). The comparison between nicotine and placebo conditions for these correlations was not significant (p=.39).

Simon Task

For MRTs of correct responses there was a main effect of Task Condition ($F_{(1,41)}$=144.34, p<.001, η_p^2=.78), revealing shorter MRTs for congruent than incongruent trials. There was no main effect of Drug (p>.14) but an interaction between Drug and Task Condition ($F_{(1,41)}$=6.77, p=.01, η_p^2=.14) (Fig. 5), indicating that MRTs were higher with nicotine than placebo in incongruent trials ($t_{(42)}$=-2.24, p=.02), but not in congruent trials (p>.25). Additionally, MRTs were higher in incongruent than congruent trials in both the nicotine ($t_{(42)}$=10.35, p<.001) and the placebo condition ($t_{(43)}$=9.66, p<.001). No other main or interaction effects were significant (all p>.09).

Regarding error rates, a main effect of Task Condition was found ($F_{(1,41)}$=19.43, p<.001, η_p^2=.32), showing that participants made fewer errors in congruent trials than in incongruent trials. There were no other main or interaction effects (all p>.16).

Correlations of MRT of congruent trials with error rate of incongruent trials were significant for both nicotine and placebo conditions (Table 4). The comparison between nicotine and placebo conditions for these correlations was not significant (p=.91).

Attention Network Test (ANT)

There were no main or interaction effects for alerting (all p>.05) or orienting (all p>.27) scores. For conflict scores, there were no main effects (both p>.09) but there was an interaction between Drug and Order ($F_{(1,42)}$=17.15, p<.001, η_p^2=.29), indicating lower conflict scores in the second than the first study session (Fig. 6). T-tests showed that these differences reached significance for both the Nic-Plc group ($t_{(22)}$=-3.65, p=.001) and the Plc-Nic group ($t_{(22)}$=2.14, p=.045). The two order groups differed significantly in their conflict scores in the nicotine condition ($t_{(42)}$=3.34, p=.003) but not the placebo condition (p=.90).

Continuous Performance Task (CPT)

For MRTs of hits, a main effect of Drug was found ($F_{(1,42)}$=4.13, p=.049, η_p^2=.09), indicating shorter MRTs with nicotine than placebo, but no main effect of Order or Drug by Order interaction (both p>.12).

Regarding false alarm rate, there were no main effects of Drug or Order and no Drug by Order interaction (all p>.09).

Correlations of MRT of hits with false alarm rate were significant for both nicotine and placebo conditions (Table 4). The comparison of these correlations between nicotine and placebo conditions was not significant (p=.29).

Baseline Dependency Effects

There was an interaction between Baseline group and Drug for ANT conflict scores ($F_{(1,38)}$=4.86, p=.03, η_p^2=.11). Post-hoc t-tests revealed that conflict scores were higher with nicotine than placebo in the high performance group ($t_{(20)}$=2.52, p=.02) but not the low performance group (p=.76), suggesting baseline dependent effects. Descriptive statistics are displayed in Supplementary Table 4.

In addition, there were three-way interactions involving Drug, Order and Baseline group for CPT percentage of false alarms ($F_{(1,28)}$=9.12, p=.005, η_p^2=.25) and Stroop percentage of errors on incongruent trials ($F_{(1,30)}$=13.65, p=.001, η_p^2=.31).

For CPT false alarms, post-hoc t-tests yielded no significant differences between nicotine and placebo in any combination of Baseline and Order groups (all p>.05). Within the Nic-Plc group, there was a difference between Baseline groups during nicotine ($t_{(14)}$=4.80, p<.001) but not placebo (p=.09). Within the Plc-Nic group, there was a difference between Baseline groups during placebo ($t_{(14)}$=3.60, p=.003) but not nicotine (p=.052). There were no differences between Order groups in either Baseline group (p>.12). Overall, this pattern shows that differences between high and low baseline performers were significant during the first but not the second study session.

For Stroop incongruent errors, post-hoc t-tests yielded significant differences between nicotine and placebo in the high performing group when receiving nicotine first ($t_{(7)}$=4.30, p=.004), but not in any other groups (all p>.12). Within the Nic-Plc group, there was a difference between Baseline groups during nicotine ($t_{(14)}$=-3.57, p=.003) but not placebo (p=.70). Within the Plc-Nic group, there were differences between Baseline groups during both placebo ($t_{(16)}$=-4.67, p<.001) and, less strongly, during nicotine ($t_{(16)}$=-2.16, p=.047). Within the high Baseline group, there was a difference between Order groups under placebo ($t_{(16)}$=3.57, p=.004) but not nicotine (p=.32). Within the low Baseline group, there were no difference between Order groups (p>.07). Overall, this pattern suggests that the above reported increase in errors from first to second study session was most pronounced for high baseline performers and that differences between Baseline groups became smaller over time.

Descriptive statistics for CPT percentage of false alarms and Stroop percentage of errors on incongruent trials are displayed by Baseline group, Drug and Order in Supplementary Tables 5-6. No other variables showed baseline dependent effects (all p>.05).

Correlations between VAS Ratings and Cognitive Variables

In the placebo condition, significant correlations were observed between MRTs on correct Stroop colour bar trials and mental sedation (r=.35, p=.02) as well as the other feelings factor (r=.31, p=.04), indicating that longer reaction times were associated with more negative feelings.

In the nicotine condition, significant correlations were observed between MRTs on correct Stroop congruent trials and mental sedation (r=.31, p=.04), physical sedation (r=.39, p=.009), tranquilisation (r=-.42, p=.005) and the other feelings factor (r=.41, p=.006). There was also a correlation of the no-go error rate on the go/no-go task with tranquilisation (r=-.34, p=.03) and of the SSRT with mental sedation (r=.35, p=.03), physical sedation (r=.35, p=.03) and the other feelings factor (r=.38, p=.02). These correlations indicated that worse performance was associated with more negative feelings.

Discussion

Using a comprehensive cognitive battery, the present study tested the effects of transdermal nicotine administration on response inhibition and interference control in healthy adults. The key findings are as follows.

First, state ratings on the VAS generally indicated negative subjective effects of nicotine. Second, nicotine was found to speed the response of prosaccades and hits in the continuous performance task without significantly improving performance in the incongruent conditions on these or any other tasks. Third, in contrast to any expected *beneficial* effects on interference control, nicotine administration led to an increased Simon effect. Fourth, there were interaction effects involving order of administration. The two key findings that emerged from these interactions were (i) nicotine-independent improvements from first to second study session, suggestive of practice effects, and (ii) order dependent effects of nicotine, suggestive of improved learning or retention of task rules when nicotine was administered first. Fifth, correlations between reaction times in congruent conditions and error rates in incongruent conditions were observed in a number of tasks, confirming assumptions of competition models. However, none of the correlations were significantly affected by nicotine. Sixth, there were some baseline dependent effects of nicotine. Finally, there were correlations between state self-ratings and performance, indicating that worse performance was associated with more negative state ratings.

Nicotine Effects on Task Performance and Subjective State Ratings

Nicotine reduced latencies of prosaccades and reaction times of CPT hits whilst not significantly affecting reaction times or error rates in any of the incongruent conditions that required inhibition or interference control. Nicotine also increased the magnitude of the Simon effect. These rather selective effects suggest that stimulation of acetylcholine receptors by nicotine primarily enhances bottom-up triggered stimulus processing. In the saccade task, such stimulation may have led to enhanced automatic triggering of the prosaccade response, and in the CPT it led to faster responses on hits.

A similar effect of nicotine may have been to enhance automatic, location-triggered response activation processes in the Simon task. The Simon task requires suppression of unwanted response tendencies to irrelevant spatial stimulus features (Hommel 2011). The effect observed here suggests that nicotine led to enhanced spatial processing of the stimulus via the automatic route (Kornblum et al. 1990), thereby causing a larger congruency effect. Importantly, this is not a beneficial effect on the intentional route translating relevant stimulus features into correct responses according to task instructions (Kornblum et al. 1990). An enhancement of control on intentional route processing would have led to the inverse result, i.e. a smaller congruency effect under nicotine. As noted previously, “cognitive costs” may be expected from cognition enhancing drugs (Goodman 2014). This should not be surprising given the known inter-relations between different aspects of cognitive performance (Bogacz et al. 2010).

Previous studies have shown that nicotine improves attention (Newhouse et al. 2004). Specifically, consistent cross-study effects of small to medium magnitude were observed on accuracy and reaction times of alerting attention and on reaction times of orienting attention (Heishman et al. 2010). Facilitatory effects on attention may have positive downstream effects on other functions such as learning and memory. However, evidence of nicotine effects on top-

down attentional control as is required in response inhibition and interference control tasks is scant (Heishman et al. 2010) and positive effects of nicotine on attention are not ubiquitous. For example, a recent study that modelled data on the basis of Bundesen's theory of visual attention (TVA; Bundesen et al. 2014) observed that nicotine improved perceptual thresholds (leading to earlier onset of stimulus processing) but reduced visual top-down attentional selectivity (Vangkilde et al. 2011). These findings are consistent with our interpretation of the current effects on faster prosaccades/CPT hits and enhanced Simon effect, respectively. Compatible with these findings, Mancuso and colleagues (1999) have previously argued that intensity aspects of attention may be improved by nicotine, without effects on attentional selectivity.

These effects on early, bottom-up aspects of attention are in line with the known neurobiology of nicotine effects, which involve agonistic action at the nicotinic acetylcholine receptor (nAChR) (Hahn 2015). In the context of attention, a particular role has been attributed to the α7 receptor subunit (Freedman 2014). An α7-nicotinic acetylcholine receptor agonist, DMXB-A (3-[(2,4 dimethoxy)-benzylidene]-anabaseine), has been shown to improve automatic attentional measures, such as sensorimotor gating, in patients with schizophrenia (Freedman 2014). Schizophrenia is a disorder known to be associated with lower cognitive performance (Schaefer et al. 2013), including deficits in measures of sensorimotor gating (Javitt and Freedman 2015). Patients with schizophrenia also show increased nicotine consumption via smoking, possibly reflecting a means of self-medicating cognitive deficits (Kumari and Postma 2005). It remains to be investigated whether improvements observed on automatic attentional measures in this study are related to nicotine effects on early gating processes.

No beneficial or adverse main effects of nicotine were observed on any of the other response inhibition or interference control tasks, although there was a non-significant trend (p=.08) towards lower error rates on the flanker task following nicotine. Whilst these generally negligible and non-significant effects on top-down attentional control are difficult to explain, the following arguments suggest that our study had sufficient power to detect beneficial effects. First, our sample size was large compared to most previous studies of nicotine effects on cognition in the published literature. Specifically, the average sample size of studies included in the meta-analysis by Heishman et al (2010) was N=24.6, with 58% of sample sizes having N≤20. A post-hoc power analysis using G*Power (Faul et al. 2007) showed that with the sample size included here we had 79% power to detect an effect size of 0.35. Second, our finding of positive nicotine effects on bottom-up triggered responses in the prosaccade and CPT paradigms underscores our argument that we had sufficient power to detect beneficial effects of nicotine. Third, we previously detected positive results of a 7mg nicotine patch on different measures of attention, inhibition and cognition in similarly selected healthy adults (Kambeitz et al.; Petrovsky et al. 2012; Schmechtig et al. 2013; Petrovsky et al. 2013b; Petrovsky et al. 2013a), suggesting that the dose and method of application as well as participant selection were well justified. Finally, as will be discussed in more detail below, there were effects of repeated exposure that resulted in performance improvements in various tasks, suggesting that performance was not at ceiling which would have prevented to find improvement through nicotine.

An important finding of this study is that subjective state ratings were generally more negative with nicotine than placebo. These negative effects contrast with the often reported subjective enhancement of alertness and mood with

nicotine in smokers (Kumari and Postma 2005) and are likely due to the fact that the current sample consisted entirely of non-smokers. Adverse effects of nicotine on mood state in non-smokers have been shown previously (Foulds et al. 1997), suggesting that positive effects observed in smokers might be due to tolerance (Perkins et al. 2003). Interestingly, more negative state ratings at the time of the start of cognitive assessment were associated with worse performance on a number of tasks, suggesting a common adverse influence of nicotine at subjective and cognitive levels.

Order Dependent Effects

Within-subjects designs with counterbalanced order of administration allow the identification of both effects of repeated exposure (or practice) and order dependent drug effects. Both are often observed in experimental pharmacological studies (Elliott et al. 1997; Ettinger et al. 2003).

For both the flanker task and the ANT, performance improved from first to second study session, indicated by shorter RTs and lower conflict scores, respectively. These effects were comparable for each of the substance groups, suggesting beneficial effects of repeated task performance. An important implication of these findings is that the current tasks had sufficient sensitivity to detect performance improvements at the level of reaction times, even in this sample of carefully screened, healthy participants. The observed, practice-related improvements thus discount the possibility that the lack of nicotine effects on measures of top-down control may have been due to ceiling effects in these tasks.

In the saccade task, there were fewer prosaccade errors in the second compared to the first study session in the group receiving nicotine first. A similar pattern was observed for the shape matching task, where reaction times were shorter in the second than the first study session in the nicotine first group only. This pattern suggests that improved learning and retention of task rules may have occurred when the task was experienced first under nicotine. Similar effects of nicotine have previously been described in the domain of perceptual learning, where nicotine administration after performance of a visual discrimination task leads to better performance at retest compared to placebo (Beer et al. 2013).

Regarding the Stroop task, whilst reaction times were generally shorter in the second than the first study session, suggesting improvements with repeated exposure, an interaction with task condition suggested that in the nicotine first group this effect was significant for incongruent and congruent trials, whereas in the placebo first group it was significant for incongruent trials. Additionally, in the nicotine first group reaction times were shorter for colour bars compared to congruent trials during nicotine, an effect that was not seen during placebo or in the placebo first group. A possible interpretation of this beneficial effect in a simple task condition could be increased arousal or selective facilitation of dimension-based attention on the colour of the target.

Interestingly, on the Stroop task there were higher error rates in the second than the first study session. This adverse effect of repeated task performance may be a consequence of the generally faster reaction times, suggestive of a repetition-induced speed-accuracy trade-off.

Generally, evidence concerning performance improvements in inhibition-related functions due to repeated exposure is mixed, with some but not all studies reporting such effects (Ettinger et al. 2003; Ishigami and Klein 2010; Wöstmann et al. 2013; Meyhöfer et al. 2015). However, faster responding on Stroop tasks following repeated performance has been found in a number of previous studies (Davidson et al. 2003; Beglinger et al. 2005; Portaccio et al. 2010; Wöstmann et al. 2013).

Baseline Dependent Effects

Previous studies have shown that the pro-cognitive effects of nicotine and other putative cognitive enhancers may show baseline dependency, that is, depend on the participants' initial performance levels (Mehta 2002). In this study, we failed to replicate our previous observation of the baseline dependency of nicotine effects on antisaccade performance using an identical 7mg transdermal nicotine patch (Petrovsky et al. 2012). Reasons for this failure to replicate may include differences in task design (blocked antisaccade/prosaccade tasks in our earlier study vs. an interleaved AS/PS task in our current study) or participant characteristics that invariably differ between studies.

However, there was evidence of baseline dependence for the ANT conflict score. This effect indicated that the group with high baseline performance worsened with nicotine relative to placebo, whereas the low baseline performance group showed no nicotine effect. This pattern may be consistent with arguments that pharmacological stimulation may be detrimental in individuals who are already at optimal levels (Husain and Mehta 2011), in concordance with earlier theories of non-linear relationships between stimulation and performance (Yerkes and Dodson 1908; Easterbrook 1959).

CPT false alarms and Stroop incongruent errors showed baseline dependent effects that interacted with order of task administration. These interactions indicated that performance differences between high and low baseline performers became smaller with repeated assessments, suggestive of regression to the mean.

Individual Differences

Correlations between error rates in incongruent conditions and reaction times in congruent conditions were observed both under nicotine and placebo for the go/no-go, CPT, flanker, shape matching and Simon tasks. These were expected within the competition or horse-race framework (Pierce and McDowell 2016; Talanow et al. 2016). Surprisingly, no significant correlation arose between prosaccade latency and antisaccade direction error rate, despite our previous observation of this relationship in larger samples (see Ettinger et al. 2005 and unpublished analysis of data in Polner et al. 2015). A possible explanation is that in our previous studies prosaccades and antisaccades were performed block-wise, whereas in this study they were performed in a mixed design.

Interestingly, there were no differences in the magnitude of the correlations for any task between the nicotine and placebo conditions. A negative relationship between congruent condition reaction times and incongruent condition errors is compatible with models of competition between bottom-up and top-down processes. As such, the observed pattern suggests that nicotine may not fundamentally alter the weight in the competition between congruent

responses and inhibition/interference control processes across individuals. This is in agreement with the finding that improvements in reaction times on the saccade task and the CPT hits were not accompanied by increases in errors, as may be expected if nicotine tipped the balance in strength between these two competing processes. This finding also suggests that the observed relationships between (congruent) reaction times and (incongruent) errors are invariant to inter-individual differences in response variability (Ettinger et al. 2009).

Limitations

A first limitation of the study is that we did not include a nicotine tolerance session. Such a session might have been useful in order to screen out participants who react adversely to nicotine. Given that we observed negative effects of nicotine in VAS ratings, it may have been of interest to limit the study of the cognitive effects of nicotine to participants who do not experience such negative subjective drug effects. A second limitation concerns the fact that only a single dose was studied. Future studies would clearly benefit from multiple doses in order to identify to which extent the observed effects are dose-dependent. Third, although the sample of this study was larger than those of many other studies in the field (Heishman et al. 2010), even larger studies with more power may be needed to reliably show the often rather subtle effects of nicotine on cognition. Finally, whilst our study addressed the effects of nicotine on top-down and bottom-up influences by drawing upon reaction times and error rates, no formal modelling of underlying processes was carried out. Such modelling would be of interest in future studies in order to provide more information on the compound's effects on the automatic and controlled processing routes that have been hypothesised to underlie performance on tasks such as the ones used here (see e.g. Ridderinkhof et al. 2005; van den Wildenberg et al. 2010).

Conclusions

To conclude, across a number of response inhibition and interference control tasks we observed beneficial effects of nicotine on two measures of bottom-up attentional processing. These effects agree with previous findings of positive nicotine influences on attention. Effects on subjective mood states, however, were generally negative in this sample of healthy non-smokers. We failed to observe, however, significant and consistent beneficial effects of nicotine on top-down control in the applied inhibitory tasks. Instead, there was evidence that nicotine worsened interference costs in the Simon tasks, possibly due to enhanced spatial processing of the stimulus via the automatic route.

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