Psychopharmacology (2009) 202:93–102
DOI 10.1007/s00213-008-1320-7

ORIGINAL INVESTIGATION

Positive effects of nicotine on cognition: the deployment of attention for prospective memory

J. M. Rusted · R. Sawyer · C. Jones · S. L. Trawley · N. L. Marchant

Received: 14 May 2008 / Accepted: 25 August 2008 / Published online: 25 September 2008

Abstract
Rationale Human and animal studies over the last two decades report that nicotine can improve cognitive performance. Prospective memory (PM), the retrieval and implementation of a previously encoded intention, is also improved by pre-administration of nicotine. As with other nicotine effects, however, predicting precisely how and when nicotine improves the processes engaged by PM has proved less straightforward.
Objective We present two studies that explore the source of nicotine's enhancement of PM. Experiment 1 tests for effects of nicotine on preparatory attention (PA) for PM target detection. Experiment 2 asks whether nicotine enhances processing of the perceptual attributes of the PM targets.
Materials and methods Young adult non-smokers matched on baseline performance measures received either 1 mg nicotine or matched placebo via nasal spray. Volunteers completed novel PM tasks at 15 min post-administration.
Results Experiment 1 confirmed that pre-administration of nicotine to non-smokers improved detection rate for prospective memory targets presented during an attention-demanding ongoing task. There was no relationship between PM performance and measures of preparatory attention. In experiment 2, salient targets were more likely to be detected than non-salient targets, but nicotine did not confer any additional advantage to salient targets.
Conclusion The present study suggests that nicotinic stimulation does not work to enhance perceptual salience of target stimuli (experiment 2), nor does it work through better deployment of preparatory working attention (experiment 1). An alternative explanation that nicotine promotes PM detection by facilitating disengagement from the ongoing task is suggested as a future line of investigation.

Keywords Nicotine · Attention · Prospective memory · Humans

J. M. Rusted (✉) · R. Sawyer · C. Jones · S. L. Trawley · N. L. Marchant
Department of Psychology, Sussex University, Brighton BN1 9QG, UK
e-mail: j.rusted@sussex.ac.uk

Present address:
S. L. Trawley
Department of Psychology, Nottingham University, Nottingham, UK

In developing interventions for age- and disease-related cognitive decline, nicotine and nicotinic analogues are persistently revisited for their pharmacological potential. This is because findings from both human and animal studies over the last two decades indicate that nicotine can improve cognitive performance, most particularly on tasks that require attention. Recent examples of the extensive human literature include studies of sustained attention and vigilance (Lawrence et al. 2002), visuospatial selective attention (Meinke et al. 2006), anti-saccade performance (Rycroft et al. 2006), spatial working memory (Green et al. 2005), associative memory (Holmes et al. 2008) and studies of covert attentional deployment (Giessing et al. 2006; Hahn et al. 2007).

A primary index of the potential therapeutic value of any cognitive-enhancing drug or family of drugs is their ability to improve everyday memory. Prospective memory (PM), simply defined, is the retrieval and implementation of a previously encoded intention to do something (e.g., an errand, a job, a favour). It is integral to the successful management of our everyday lives, and as we get older, we can reliability anticipate that this ability will decline (Maylor 1993; Henry et al. 2004; Logie et al. 2004). PM

is not a single process, but a composite of attentional and memorial engagement. Consistent with the engagement of attention as a prerequisite for effective PM, pre-administration of nicotine improves PM performance (Rusted et al. 2005; Rusted and Trawley 2006; Marchant et al. 2008). As with other nicotine effects, however, predicting precisely how and when nicotine improves the cognitive processes engaged by PM is not simple. In this paper, we present experimental data exploring possible routes by which nicotine might improve PM.

Paradigms designed to study PM have most commonly explored event-based prospective memory. In this situation, a predesignated PM target cue is established, and volunteers are required to execute an associated 'intention' whenever the target is detected. An ongoing cover task is employed to engage attention and to introduce the prerequisite delay between encoding the intention-target association and the retrieval opportunity (self-initiated on detecting the target cue within the ongoing task). In PM, the effort of maintaining an intention can be measured as a cost to performance (in accuracy or time) in the ongoing task. This cost and the conditions that modulate it have been the focus of a large number of studies and a theoretical division between PM researchers.

A widely accepted model of PM (McDaniel and Einstein 2000; McDaniel et al. 2004; Einstein and McDaniel 2005) suggests that while a PM target may be actively maintained and occupy attentional resources, attention is not inevitably implicated in PM processing. Critically, these researchers argue that certain conditions promote automatic or 'reflexive' target cue activation (e.g. when the target is identified as part of the ongoing task or when the target is made physically salient), allowing retrieval without active engagement of attention and hence without cost to ongoing processing (McDaniel et al. 2004; Einstein and McDaniel 2005). Their multiprocess framework (McDaniel and Einstein 2000) describes a continuum of situations with negligible to full engagement of attention to detection of the target cue, but specifically includes evidence for a zero-cost 'automatic' reactivation of PM intentions in response to appearance of the target item. This, they suggest, marries with the subjective experience of PM intentions popping back into mind at the key time for implementation.

Smith (Smith 2003; Smith and Bayen 2004), in contrast, takes the position that although the cost may vary (see Smith et al. 2007 for a review of the conditions that promote most and least cost), attention always is engaged when an intention is encoded and always will produce a measurable cost to ongoing activities until the intention is implemented. This position attributes significance to the ongoing task cost (termed 'preparatory attention') as an index of attentional deployment (Smith 2003), under the assumption that any monitoring for the PM targets will decrease resources directed at the ongoing task. The current PM data, however, are equivocal on this issue. Although maintaining an intention can impair (in accuracy or time) performance on the ongoing task (see Smith et al. 2007), this cost to ongoing task performance seems to depend on individual resource allocation policies established at the point of encoding of the intention (Marsh et al. 2006; Hicks et al. 2005). In addition, while overt attention allocation may underwrite the preparatory attention effect (e.g. WM capacity affects the PM cost to the ongoing task; Marsh and Hicks 1998; Smith 2003), the ongoing task cost does not always predict PM accuracy (Hicks et al. 2005; West et al. 2005; Marsh et al. 2006; McNerney and West 2007). In short, the relationship between PM accuracy and preparatory attention is not well characterised by data from cognitive studies, and the critical significance of preparatory attention (PA) to PM accuracy remains unclear.

Psychopharmacological studies may help to resolve this issue. PM accuracy is reliably improved by pre-administration of nicotine, and this is true for both nicotine users and nicotine-naïve volunteers (Rusted et al. 2005; Rusted and Trawley 2006, Marchant et al. 2008). The first of these studies included a measure of the cost of carrying an intention: Volunteers completed the ongoing task (lexical decision) both with and without an embedded PM intention. Nicotine, while improving overall detection rate of PM targets, did not influence the RT cost of carrying the intention [mean RT (LDT+PM)−mean RT (LDT only)]. This implies that preparatory attention, as it is currently measured, may not be a critical factor in determining PM performance and that the simple hypothesis that nicotine improves PM by improving preparatory attention is clearly inaccurate.

Perceptual salience is a feature that multimodal PM theorists have associated with automatic activation of targets—if a target is perceptually salient, it is likely to be detected without the active allocation of attentional resource (McDaniel and Einstein 2000). According to this position, nicotine would not be expected to enhance the detection of salient targets since nicotine improves performance on attention demanding but not automatic processing (Robbins 2002; Levin et al. 2006; Kumari and Postma 2005, for recent reviews of the cognitive effects of nicotine). In contrast, Smith et al. (2007) argue that perceptual salience signals a perceptual difference between successive events that cannot, of itself, inform the detection of prespecified target items. Accordingly, they argue that there is an attentional cost even for highly salient targets, and nicotine would be predicted to increase target detection for both target types.

In the psychopharmacology literature, perceptual salience is associated with signal-driven processing, and there

is good evidence for cholinergic engagement in such bottom-up processes of stimulus detection. This is seen in nicotine-induced shift in the P300 ERPs associated with registration of novel stimuli (Edwards et al. 1985), faster letter detection RTs (e.g. Kerr et al. 1991) and faster identification times for targets in a memory scanning task (e.g. West and Hack 1991). There is evidence for top-down modulation of attention by cholinergic systems too, with augmented cholinergic release in the prefrontal cortex in response to increased task demands (Kozak et al. 2006; Parikh et al. 2008). The critical question, however, is the relative contribution and interdependence of the top-down and bottom-up cholinergic systems in determining where and how we allocate attention in a busy and demanding environment (Sarter et al. 2005; Parikh et al. 2008).

Furey et al. (2000) reported that administration of a cholinergic agonist (physostigmine) prior to completion of a visual working memory task selectively increased BOLD activation in the ventral extrastriate cortex (decreasing activation in the anterior prefrontal cortex). They interpreted this result as evidence for localisation of cholinergic enhancement at a perceptual processing level, reducing the load on top-down (that is frontal) engagement. This interpretation is not consistent with the PM data reported by Rusted and Trawley (2006), where nicotine did not protect PM detection rate when volunteers were required to perform a concurrent working memory task. More recently, Hahn et al. (2007) demonstrated that nicotine-related benefits in a covert orienting paradigm (nicotine speeds RTs to targets appearing in non-cued locations) were larger for perceptually salient (high contrast) targets relative to low contrast targets. These authors suggested that nicotine promotes the reallocation of resources to the task in hand and that this is achieved in part through maintaining the "alerting properties of task-relevant stimulus attributes". We interpret this to mean that nicotine promotes processing of perceptual features of the relevant stimulus and that increasing perceptual distinctiveness of those targets will potentiate this advantage. Applying these findings back to PM, both the Furey and Hahn results imply that nicotine will potentiate a saliency advantage. This is in contrast to the McDaniel Einstein position that nicotine will only advantage non-salient targets, and the Smith position, that nicotine will have no differential effect on a saliency manipulation.

In this paper, we present two studies that explore the source of nicotine's enhancement of PM. In the first study, we re-examine nicotinic effects on preparatory attention. In the second study, we manipulate salience of the PM targets and directly test the predictions derived from the different theoretical positions described earlier.

Methods: experiments 1 and 2

Participants

Experiment 1 Thirty-three non-smoking[1] volunteers were recruited at Sussex University, 21 females and 12 males, age ranging from 18 to 31 years old (*M* 22 years, SD 3.3). Inclusion criteria included BMI in normal range, no current medication (excluding the contraceptive pill), blood pressure in normal range and no history of heart problems. All participants volunteered under a written informed consent procedure approved by the Sussex University School of Life Sciences Ethics Committee. Participants were reimbursed for their participation.

Experiment 2 Sixty non-smoking participants from Sussex University, with a mean age of 21 years (SD 2.05; range 18–29) took part in the study. Inclusion criteria remained the same as in experiment 1.

Design: experiment 1

The experimental design involved two sessions, one nasal spray familiarisation session and one experimental session. In a double-blind procedure, volunteers were randomly assigned to receive either 1 mg nicotine or placebo, delivered in valence-matched nasal spray, coded by an independent third party. In the experimental session, all volunteers completed the same ongoing card-sort task without and with an embedded PM task. Accuracy and RTs for the ongoing task and PM accuracy provided the dependent measures. In addition, subjective indices of mood change contingent upon using the nasal sprays were monitored at intervals across the session using Bond and Lader (1974) mood scales. Baseline tests of immediate memory were used to ensure comparability of the sample across drug conditions.

Design: experiment 2

As for experiment 1, the study involved one familiarisation session and one experimental session. In a double-blind procedure, volunteers were randomly assigned to receive either 1 mg nicotine or placebo, delivered in valence-matched nasal spray, coded by an independent third party. In the experimental session, all volunteers completed an ongoing mental math task with an embedded PM task. Drug condition (nicotine/placebo) was a between-subjects factor, and the target type (salient/non-salient) was a within-

[1] Non-smokers were defined as never-smoked or not smoked (cigarettes) for at least 5 years.

subject factor, producing a 2×2 mixed factorial design. Accuracy and RTs for the ongoing task and PM accuracy provided the dependent measures. In addition, mood change contingent upon using the nasal sprays were monitored at intervals using Thayer (1989) mood scales; blood pressure was monitored at the same time points. Baseline tests of immediate memory were used to test for comparability of the sample across drug conditions.

Materials: experiments 1 and 2

Nasal sprays

Nasal sprays comprised individual bottles with mechanical spray pumps that delivered 0.5 mg of nicotine or a matched inactive placebo per spray. Each volunteer self-administered two sprays, one in each nostril, delivering 1.0 mg nicotine or matched placebo. Peak plasma levels are reached 15 min after delivery (Schneider et al. 1996). The sprays were provided by AB McNeil, Helsingborg, Sweden.

Baseline tests

A word list comprising 20 words was presented at a rate of 2 s per word on a computer screen for immediate written free recall.

Subjective and physiological measures

In experiment 1, Bond and Lader (1974) visual analogue mood scales were completed before and 15 min after the nasal spray was administered. From the 16 individual Bond–Lader mood scales, a mean score for each of the four factors were derived [contentedness, attentiveness, calmness and physical competence (not reported)] for both time points. In experiment 2, subjective measures of arousal were taken (at three time points: baseline, 15 and 30 min post drug) using the Thayer (1989) scale; this scale contains 20 adjectives on a four-point scale to describe energetic vs tense arousal. Blood pressure measures were taken on each occasion immediately before completion of the Thayer scales.

Experimental test: experiment 1

The ongoing task comprised a card sort, using images of a regular set of playing cards, generated on the computer screen. For each trial, the back of the card appeared for 1,000 ms, reversing to show the face card for 750 ms, advancing automatically between cards. Volunteers were instructed to complete a sort task as the cards were turned over. Using a three-button box, they were instructed to press the left button when the card was a HEART and the right button when the card was a CLUB. They were instructed to withhold responses (i.e. make no response) if the cards were SPADES or DIAMONDS. In addition, volunteers were told that for any number 7 cards, independent of suit, they were to press the middle button, rather than making a sort/withhold response. This constituted the PM intention. The instructions were followed by a series of eight practice 'sort' trials, with no PM targets. For the experimental trials, two full decks of 52 playing cards (104 in total) were randomly presented, in two blocks (prefaced by "first deck", "second deck" labels). The 4 target cards were distributed quasi-randomly in each deck, making a total of eight PM targets in 104 trials. Finally, volunteers were asked to sort hearts and clubs from a third deck of 52 cards, this time without making special responses to the 7s; this provided the baseline measure for sort speed and accuracy when not carrying a PM intention. The software (MATLAB) recorded the response time and accuracy of each button press.

Experimental test: experiment 2

The ongoing task was a mental maths task. For each trial, a simple sum was presented on the computer screen for 500 ms; each sum involved a multiplication, division, subtraction or addition of two digits between 1 and 9 (excluding the digit 2) and an answer. The sum presented was either correct (e.g. 3+3=6) or incorrect (e.g. 4×3=11). Participants were required to press a green button if they thought the sum was correct and a red button if they thought it was incorrect. There were a total of three blocks, each containing 40 sums. Volunteers had a 30-s break between each block, with the end of the break signalled by an auditory 'beep' and a 'get ready' prompt. The embedded PM task involved monitoring the sums for the presence of the digit 2, pressing the spacebar to register an occurrence. Participants were told that this target number could appear anywhere within the sum, although in practice it only appeared in the answer, and always as part of a two-digit number (e.g. 12, 21, etc.). There were two targets per block (six targets in total over 120 trials). For the saliency manipulation, half of the sums that contained a target were presented in the same font size (12) as the rest of the sums, and half were displayed in a larger font size (20). The instructions for the task did not mention the variation in font size. The experimental sequence began with a series of 12 practice trials, none of which contained a PM target. The software (Psyscope) recorded the response time and accuracy of each button press.

Table 1 Experiment 1: summary table showing means and standard deviations for baseline measures by condition

Condition		Nicotine, mean (SD)	Placebo, mean (SD)
Baseline measures	Immediate free recall	10.19 (3.64)	10 (2.67)
	BMI	22.1 (2.3)	22.4 (1.9)
	Age	22.2 (2.9)	21.9 (3.7)
Bond and Lader mood scales: baseline	Alertness	53.33 (16.83)	48.76 (15.17)
	Calmness	54.63 (12.59)	53.04 (9.59)
	Contentedness	64.94 (10.56)	62.04 (11.45)
Bond and Lader mood scales: 15 min post-spray	Alertness	57.67 (18.22)	49.81 (14.06)
	Calmness	55.22 (8.76)	56.62 (6.96)
	Contentedness	66 (11.41)	62.12 (10.98)

Procedure: experiment 1

A preliminary session (1–3 days before the experimental session) familiarised participants with administration and sensory experience of the nasal spray. In addition, participants completed the baseline word recall task. The experimental session began with a Bond and Lader (1974) mood scale. Instructions for and a practise of the card sort were then completed. Eight practice cards were presented. No target items appeared in the practice cards. Subsequently, the participant self-administered the nasal spray (one puff in each nostril) and completed simple cognitive filler tasks for a period of 15 min (to peak plasma level). The participant was then asked to complete a second Bond and Lader (1974) scale, followed by the card sort with embedded PM task (two decks). No reminders were provided of the task instructions at this point. Instructions regarding the third deck were provided after completion of the second deck, instructing participants only to sort the cards into the appropriate categories for the final deck. Subsequent to the final trial, instructions on the screen prompted the volunteer to repeat back to the experimenter all of the instructions that were originally given.

Procedure: experiment 2

As in experiment 1, all volunteers completed a preliminary familiarisation. The experimental session began with baseline (t0) BP measures and the Thayer mood scales. Participants then self-administered the nasal spray and completed filler cognitive tasks, including the NART, for 15 min. They then completed a second Thayer scale and blood pressure (t1) before going onto the main prospective memory task. Piloting on this task confirmed that positioning of instructions immediately before onset of the task produced the appropriate level of performance (approximately 50% of PM targets reported). The experimenter provided written instructions for the task and checked that the volunteers understood these instructions before instigating a set of 12 practice trials. Volunteers then completed the full experimental task under automated conditions. After completing the task, participants were asked to recall the instructions given at the start of the task in order to check their understanding of what was required of them. They completed a final Thayer scale and blood pressure (t2) and were asked to say whether they thought they had received nicotine or a placebo spray.

Results and discussion

Results: experiment 1

Preliminary analyses

Independent sample t tests revealed that participants across conditions were matched on age, (t (31)=0.209, p>0.05), gender, (t (31)=0.128, p>0.05), body mass index (t (31)= −0.385, p>0.05) and baseline memory test scores [F(1,31)= 1.574, p>0.05; Table 1].

Experimental task

All volunteers were able to correctly repeat back the PM instructions at the end of the ongoing task performance, indicating that they had encoded the requirement to respond to PM targets during the ongoing task. Mean performance measures for the card-sort task are shown in Table 2.

Ongoing card-sort accuracy during PM task A two-way mixed factorial ANOVA compared sort and withhold accuracy across drug condition. Volunteers made significantly more sort errors than withhold errors [F(1,31)=7.38,

Table 2 Experiment 1: means and standard errors for the card-sort task with and without a PM intention and with and without nicotine

Condition	Nicotine, mean (SE)	Placebo, mean (SE)
PM target detections (max=8)	5.06 (1.57)	3.82 (1.38)
% cards correctly sorted with PM intention	85.93 (4.04)	90.19 (3.92)
% card responses correctly withheld with PM intention	96.34 (1.17)	94.60 (1.14)
% cards correctly sorted without PM intention	88.48 (4.29)	90.96 (4.16)
% card responses correctly withheld without PM intention	98.81 (1.26)	96.17 (1.22)
Mean sort RT with PM (ms)	637 (16)	623 (15)
Mean sort RT without ProM (ms)	570 (15)	577 (14)

p=0.011]. There was no effect of nicotine (F<1) and no interaction with response type.

Ongoing card-sort reaction times during PM task For sort RTs completed with a PM intention, mean RTs were unaffected by nicotine (F<1).

PM target detection In a one-way analysis of PM accuracy, volunteers who received nicotine detected significantly more PM targets than volunteers receiving placebo [F(1,31)=5.819, p=0.022].

Preparatory attention: the cost of carrying an intention Ongoing task accuracy (calculated as percent of cards correctly sorted and withheld) was better for deck three (without PM intention) compared to decks one and two [with PM intention; F(1,31)=6.56, p=0.016]. There was no effect of drug and no interaction between factors (F's<1). Card-sort RTs were significantly faster when there was no PM load (deck 3) compared to decks one and two (with PM load) [F(1,30)=40.6, p<0.001], again indicating a cost to RTs resulting from the requirement to monitor PM targets. There was no effect of drug on RTs and no effect of drug on the size of the PM cost (F's<1.4). There was no correlation between cost and PM detection rate, between ongoing task accuracy and PM performance or between ongoing task RTs and PM performance.

Arousal measures

Subjective effects of nicotine Three two-way repeated measures ANOVAs on the Bond and Lader factors of contentedness, calmness and alertness indicated no significant changes in mood over time (pre–post spray), no effects of spray type on mood and no interactions (all F's<1).

Summary: experiment 1

The results of this study confirmed, in a new paradigm, that pre-administration of nicotine to non-smokers improved their detection rate for prospective memory targets presented during an attention-demanding ongoing task. Completion times for the same task undertaken without the PM component demonstrated that there was an attentional cost to maintaining the PM intention. This cost has previously been associated with anticipatory attention to the detection of PM targets, defined as preparatory attention. Critically, in the present study, this measure of attentional cost was not modulated by nicotine, despite the nicotine-induced improvement in PM detection rate. This result confirmed previous findings (Rusted et al. 2005) and once again questioned the significance of the relationship between preparatory attention and PM accuracy. In the present study, there was no relationship between PM performance and any measure of PA. The enhancing effects of nicotine on PM in this instance did not derive from improved preparatory attention.

Experiment 2 considered whether the positive effects of nicotine on PM detection were associated with enhanced processing of perceptual attributes of the target items.

Results: experiment 2

Preliminary analyses

There were no group differences between participants assigned to the nicotine and placebo conditions, either in age, NART IQ, immediate free recall, baseline tense or energetic arousal, or baseline blood pressure (independent t tests: all ps>0.1; Table 3).

Arousal measures

Table 4 shows the data for subjective and physiological measures over the session. Two-way mixed ANOVAs (2 (placebo/nicotine)×3 (baseline, t1, t2)] were performed separately for tense arousal, energetic arousal and mean arterial blood pressure.

Subjective arousal There was no effect of group on tense [F(1,58)=2.521, p>0.05] or energetic [F(1,58)=2.053, p>0.05] arousal measures, no effects of time and no interactions between the two factors (F's<1), indicating no differential effect of nicotine on either measure.

Physiological arousal There was no main effect of group on mean arterial blood pressure [F(1,28)=1.50, p>0.05], no change over time [F(2,56)=1.70, p>0.05] and no interaction between factors (F's<1).

Table 3 Experiment 2: summary table showing means and standard deviations for baseline measures by condition

	Nicotine, mean (SD)	Placebo, mean (SD)
Age (years)	21.6 (2.4)	20.9 (1.6)
Verbal IQ	112 (6.7)	114 (7.0)
Word recall	6.93 (1.87)	7.30 (2.35)
Mean arterial BP	95.62 (11.8)	100.27 (14.9)
Tense arousal	3.09 (3.69)	2.00 (1.44)
Energetic arousal	4.76 (4.60)	3.17 (2.90)

Table 4 Experiment 2: mean subjective and physiological arousal indices over time for nicotine and placebo treatments

		Nicotine		Placebo	
		Mean	(SD)	Mean	(SD)
Thayer energetic arousal scale	Baseline	4.76	(4.60)	3.17	(2.90)
	T1: 15 min post-spray	4.79	(4.46)	3.51	(3.31)
	T2: 30 min post-spray	4.53	(4.53)	3.24	(2.66)
Thayer tense arousal scale	Baseline	3.09	(3.69)	2.01	(1.44)
	T1: 15 min post-spray	3.18	(3.64)	1.94	(1.43)
	T2: 30 min post-spray	3.15	(3.59)	2.09	(1.69)
Mean arterial BP	Baseline	96.19	(11.19)	100.27	(14.88)
	T1: 15 min post-spray	91.72	(10.36)	98.63	(13.75)
	T2: 30 min post-spray	92.93	(12.56)	97.40	(13.94)

Experimental task

Ongoing task: mental maths accuracy There was no effect of drug on participants' ongoing task performance (t (58)= 0.860, $p>0.05$; Table 5). Volunteers were more likely to answer correctly when the correct response was 'yes' than when it was 'no' [$F(1,58)=78.19$, $p<0.05$], but this was independent of nicotine condition (F's<1).

Ongoing task: mental maths RTs A 2 (nicotine/placebo)×2 (correct yes/correct no) mixed factorial ANOVA on RTs to correct yes and correct no mental maths revealed no significant effects of nicotine and no interactions with nicotine. RTs were slower when the correct response was no [$F(1,58)=19.21$, $p<0.001$; Table 5).

PM target detection All volunteers were able to correctly repeat back the PM instructions at the end of the ongoing task performance, indicating that they had encoded the requirement to respond to targets during the PM task. Nevertheless, 32 out of 60 participants failed to detect a single target, despite reporting back the instructions accurately as a post-task requirement. PM researchers have debated the best approach to non-responders. Some have argued that these individuals may have remembered the instructions when prompted, but this does not guarantee that they implemented them during the task. In the PM literature, habitually up to 20% of volunteers may fail to identify any PM targets. For the current study, we are unable to differentiate poorly motivated volunteers from volunteers who just failed to detect the PM targets, so exclusion is difficult to justify on these grounds. In addition, the ongoing task was a challenging one, involving mental maths. It is likely that this contributed to the poor PM detection rate; volunteers scoring no PM hits were significantly worse at the ongoing task (means 70.8% vs 77.1% respectively, $p<0.05$), suggesting that for these volunteers, the ongoing task drew resources away from the PM task. Mixed 2×2 factorial ANOVAs completed both on the full 60 participants and on the 28 individuals with at least one PM response produced an identical pattern of results (Table 6). This supports our view that the data were not compromised by the poor PM response rate. For brevity, only the former is presented.

A 2 (nicotine/placebo)×2 (salient/non-salient targets) mixed factorial ANOVA on PM detection rate revealed a marginal main effect of drug [$F(1,58)=3.233$, $p=0.077$], indicating that regardless of whether the targets were salient or non-salient, participants who were given nicotine identified a higher percentage of targets than those in the placebo condition (Table 5). There was a significant main effect of saliency on PM performance [$F(1,58)=6.564$, $p<0.05$], with salient targets more likely to be detected (Table 6). Critically, there was no significant interaction between drug and saliency conditions [$F(1,58)=0.103$, $p>0.05$]: nicotine did not differentially benefit salient targets.

Summary: experiment 2

In experiment 2, the ongoing task was a mental maths task. This was developed to provide a suitable environment for a perceptual salience manipulation. Volunteers completed the ongoing task while maintaining the PM intention to detect all occurrences of the digit '2'. In practice, the digit was

Table 5 Experiment 2: mean (with standard errors) performance in the ongoing mental maths task across conditions

Condition	Nicotine, mean (SE)	Placebo, mean (SE)
Overall % accuracy mental maths	74.99 (2.12)	72.42 (2.12)
Mean RTs to correct 'yes' responses	1,107 (32.6)	1,062 (32.7)
Mean RTs to correct 'no' responses (ms)	1,227 (41.0)	1,149 (41.0)

Table 6 Experiment 2: mean percentage (with standard errors) of non-salient and salient target detections across conditions

Condition	Non-salient, mean (SE)	Salient, mean SE)	Overall, mean (SE)
Nicotine, $n=30$	24.45 (5.75)	34.45 (7.23)	27.36 (6.04)
Placebo, $n=30$	12.22 (4.07)	20.00 (5.67)	16.11 (4.19)
Conservative sample			
Nicotine, $n=16$	45.838 (7.38)	64.588 (7.74)	51.294 (7.09)
Placebo, $n=12$	30.550 (7.63)	49.992 (8.71)	40.283 (5.21)

always presented as a member of a composite two-digit number[2]. The results of experiment 2 were clear cut. We observed a positive but small improvement in PM detections under nicotine. There was a highly significant effect of perceptual salience, with salient targets more likely to be detected than non-salient targets. Critically, there was no interaction between drug condition and salience: Nicotine did not confer any additional advantage on salient compared to non-salient targets.

Discussion

The primary aim of the studies reported here was to examine nicotinic facilitation of prospective memory performance, and the focus of the discussion will be on this aspect of the study. The two studies reported here also have implications for current theoretical models of prospective memory, however, and these will be summarised first.

In experiment 1, the data showed, independent of drug treatment, no correlations between PM detection and measures of preparatory attention or measures of ongoing task accuracy. This weakens the proposed relationship of PA to PM, as have previous studies (Rusted et al. 2005; Hicks et al. 2005; West et al. 2005; Marsh et al. 2005; McNerney and West 2007). The non-linearity of PA to PM trade-off clearly indicates that PM detection must engage attentional processes in addition to those under the control of the central executive/working memory that regulate overt strategic allocation of limited attentional resources.

In experiment 2, the perceptual salience manipulation increased PM detection rates. Critically, however, detection rates were very modest in this study and even for the salient targets, it did not approach ceiling. This questions the position that perceptually salient targets involuntarily and automatically capture attention (McDaniel and Einstein 2000). Our results favour the Smith et al. (2007) position that salience does not of itself guarantee detection and that PM activation independent of stimulus type will always engage attention. Since the PA/PM relationship is weak, a complete model of event-based PM must consider alternative indices of attention and performance to produce an adequate description of the behavioural data. How do the observed effects of nicotine on PM help to define the processes engaged by PM?

In experiment 1, nicotine administration significantly increased PM detection rate without inducing any corresponding changes in performance measures on the ongoing filler task. The novel card-sort paradigm was designed to engage attentional resources in the ongoing and PM elements. Confirming this, comparing performance on the same card-sort task with and without a PM component demonstrated a significant cost to RT. This indicated that carrying a PM intention diverted resources from the ongoing task. So, preparatory attention was observed, but was not modulated by nicotine. Since nicotine did enhance PM detection rate, we must conclude that nicotine does not promote PM by acting on preparatory attention, as defined by Smith and Bayen (2004).

In experiment 2, we reported a positive effect of nicotine on PM detections in a second novel paradigm, though the effect was small. In addition, half of the PM targets were made perceptually salient (appearing in a larger font size), and these were randomly interspersed with non-salient targets. Perceptual changes were not indicated in the instructions. We found that volunteers were significantly more likely to detect the perceptually enhanced targets, but that the effect of nicotine on PM performance did not interact with the effect of saliency.

In their fMRI study, Furey et al. (2000) recorded improved response times to task-relevant stimuli, alongside reduced prefrontal cortex activity and increased activity in extrastriate visual areas following administration of physostigmine. They concluded that cholinergic stimulation induced "a more vivid or distinct visual percept (of the relevant stimulus) that is easier to maintain in WM". Hahn et al. (2007) similarly reported that perceptually salient (high contrast) cues potentiated the nicotine-related benefits for target RTs in their covert orienting paradigm. They concluded that nicotine promotes the 'alerting properties' (i.e. perceptual salience) of task-relevant stimulus attributes. In contrast, our results do not argue for a perceptual explanation of the nicotine-related improvements in PM.

The absence of a nicotine×perceptual salience interaction may reflect the sensitivity of the measure used in the present study. Furey et al. (2000) used accuracy and RT measures of performance, and the nicotine effects were limited to the RT data. The study of Hahn et al. (2007) measured RTs to the target stimuli. In the present PM study, the PM targets are by necessity very low frequency occurrences, and this precludes the use of the RT data to these items; if volunteers had detected all PM targets, this would still provide only three salient and three non-salient trials per volunteer. It is possible, therefore, that nicotine did potentiate detection RT for perceptually salient stimuli, but we then would have to conclude that detection speed does not translate into improved accuracy. So again, this

[2] A central tenet of the multi-process model of PM is the argument that embedding the digit in this way precludes the automatic detection of the target as a by-product of ongoing task performance (McDaniel and Einstein 2000). According to these authors, salience promotes automatic detection, so automatic access will be confined to the salient stimulus condition.

would not support a perceptual basis for the enhanced PM detection rate under nicotine.

Phillips et al. (2000), working on an animal model of attentional orienting, have argued that nicotine facilitates the disengagement of attention from a cued location following the onset of a target in an unexpected/non-cued location. There is evidence from other studies that nicotine can facilitate disengagement of attention from task-irrelevant stimuli. Rycroft et al. (2006) reported faster response times and fewer errors on an anti-saccade task following nicotine administration, consistent with improved inhibition of the prosaccadic eye movements in response to the onset of the stimulus. Rusted and Alvares (2008) reported better inhibition of task-irrelevant word stimuli following nicotine administration in a retrieval-induced forgetting paradigm. This is an area that has not been explored directly in the PM literature, although a finding reported by Rusted et al. (2005) provides an interesting starting point; in this study, nicotine only facilitated PM performance when PM target detection required processing distinct from that required by the ongoing task—that is processing that involved some level of disengagement from the ongoing task. Kliegel (Kliegel and Jäger 2006; Kliegel et al. 2007) also has noted that PM performance in older adults is predicted by their Stroop inhibition scores, but not by a speed of processing measure. In the context of nicotinic stimulation and PM, then, nicotinic effects may be localised in the processes that govern top-down disengagement of attention from the ongoing task. We suggest that this stage of the PM process warrants systematic examination.

In conclusion, the present study suggests that nicotinic stimulation does not work to enhance perceptual salience of target stimuli (experiment 2), nor does it work through better deployment of preparatory (working) attention (experiment 1). It seems likely that such strategic engagement is not a necessary condition for the enhancement of prospective memory by nicotinic stimulation. This would be good news for the potential of nicotinic analogues as cognitive enhancers in older adults, who are notably less likely to actively apply strategic attention or memorial processes in a timely manner to improve performance (Craik et al. 1995; Maylor 1993; Schaeffer et al. 1998).

Acknowledgements We thank McNeil AB, Helsingborg, Sweden for providing the nasal sprays.

References

Bond A, Lader MH (1974) The use of analogue scales in rating subjective feelings. Br J Med Psychol 47:211–218

Craik FIM, Anderson N, Kerr S, Li K (1995) Memory changes in normal aging. In: Baddeley AD, Wilson B, Watts FN (eds) Handbook of memory disorders. Wiley, New York, pp 211–241

Edwards JA, Wesnes K, Warburton DM, Gale A (1985) Evidence of more rapid stimulus evaluation following cigarette smoking. Addict Behav 10:113–126

Einstein GO, McDaniel MA (2005) Prospective memory: multiple retrieval processes. Curr Dir Psychol Sci 14:286–290

Furey ML, Pietrini P, Haxby JV (2000) Cholinergic enhancement and increased selectivity of perceptual processing during working memory. Science 290:2315–2319

Giessing C, Thiel CM, Rosler F, Fink GR (2006) The modulatory effects of nicotine on parietal cortex activity in a cued target detection task depend on cue reliability. Neuroscience 131:853–864

Green A, Ellis KA, Ellis J, Bartholomeusz CF, Ilic S, Croft RJ, Phan KL, Nathan PJ (2005) Muscarinic and nicotinic receptor modulation of object and spatial n-back working memory in humans. Pharmacol Biochem Behav 81:575–584

Hahn B, Ross TJ, Yang Y, Kim I, Huestis MA, Stein EA (2007) Nicotine enhances visuospatial attention by deactivating areas of the resting brain default network. J Neurosci 27:3477–3489

Henry JD, MacLeod MS, Phillips LH, Crawford JR (2004) A meta-analytic review of prospective memory and aging. Psychol Aging 19:27–39

Hicks JL, Marsh RL, Cook GI (2005) Task interference in time-based, event-based, and dual intention prospective memory conditions. J Mem Lang 53:430–444

Holmes AD, Chenery HJ, Copland DA (2008) Transdermal nicotine modulates strategy-based attentional semantic processing in non-smokers. Int J Neuropsychopharmacol 11:389–399

Kerr JS, Sherwood N, Hindmarch I (1991) Separate and combined effects of the social drugs on psychomotor performance. Psychopharmacology 104:113–119

Kliegel M, Jäger T (2006) Delayed-execute prospective memory performance: the effects of age and working memory. Dev Neuropsychol 30:819–843

Kliegel M, Martin M, McDaniel MA, Phoillips LH (2007) Adult age differences in errand planning: the role of task familiarity and cognitive resources. Exp Aging Res 33:145–161

Kozak R, Bruno JP, Sarter M (2006) Augmented prefrontal acetylcholine release during challenged attentional performance. Cereb Cortex 16:9–17

Kumari V, Postma P (2005) Nicotine use in schizophrenia: the self medication hypothesis. Neurosci Biobehav Rev 29:1021

Lawrence NS, Ross TJ, Stein EA (2002) Cognitive mechanisms of nicotine on visual attention. Neuron 36:539–548

Levin ED, McClernon JF, Rezvani AH (2006) Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. Psychopharmacology 184:523–539

Logie R, Maylor E, Della Sala S, Smith G (2004) Working memory in event- and time-based prospective memory tasks: effects of secondary demand and age. Eur J Cogn Psychol 16:441–456

Marchant NL, Trawley S, Rusted JM (2008) Prospective memory or prospective attention: physiological and pharmacological support for an attentional model. Int J Neuropsychopharmacol 11:401–411

Marsh RL, Hicks JL (1998) Event-based prospective memory and executive control of working memory. J Exper Psychol Lear Mem Cogn 24:336–349

Marsh RL, Hicks JL, Cook GI (2005) On the relationship between effort toward an ongoing task and cue detection in event-based prospective memory. J Exper Psychol Learn Mem Cogn 31:68–75

Marsh RL, Cook GI, Hicks JL (2006) An analysis of prospective memory. Psychol Learn Motiv 46:115–153

Maylor EA (1993) Aging and forgetting in prospective and retrospective memory tasks. Psychol Aging 8:420–428

McDaniel MA, Einstein GO (2000) Strategic and automatic processes in prospective memory retrieval: a multiprocess framework. Appl Cogn Psychol 14:S127–S144

McDaniel MA, Guynn MJ, Einstein GO, Breneiser J (2004) Cue-focused and reflexive-associative processes in prospective memory retrieval. JEP: Learn Mem Cogn 30:605–614

McNerney MW, West R (2007) An imperfect relationship between prospective memory and the prospective interference effect. Mem Cognit 35:275–282

Meinke A, Thiel CM, Fink GR (2006) Effects of nicotine on visuospatial selective attention as indexed by event-related potentials. Neuroscience 141:201–212

Parikh V, Man K, Decker MW, Sarter M (2008) Glutamategic contributions to nicotinic acetylcholine receptor agonist-evoked cholinergic transients in the prefrontal cortex. J Neurosci 28:3769–3780

Phillips JM, McAlonan K, Robb WGK, Brown VJ (2000) Cholinergic neurotransmission influences covert orientation of visuospatial attention in the rat. Psychopharmacology 150:112–116

Robbins TW (2002) The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. Psychopharmacology 163:362–380

Rusted JM, Alvares T (2008) Nicotine effects on retrieval-induced forgetting are not attributable to changes in arousal. Psychopharmacology 196:83–92

Rusted JM, Trawley S (2006) Comparable effects of nicotine in smokers and nonsmokers on a prospective memory task. Neuropsychopharmacology 31:1545–1549

Rusted JM, Trawley S, Kettle G, Walker H (2005) Nicotine improves memory for delayed intentions. Psychopharmacology 182:355–365

Rycroft N, Rusted JM, Hutton SB (2006) The antisaccade task as an index of sustained goal activation in working memory: modulation by nicotine. Psychopharmacology 188:521–529

Sarter M, Hasselmo ME, Bruno JP, Givens B (2005) Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. Brain Res Rev 48:98–111

Schaeffer EG, Kozak MV, Sagness K (1998) The role of enactment in prospective remembering. Mem Cogn 26:644–650

Schneider NG, Lunell E, Olmstead RE, Fagerstrom K (1996) Clinical pharmacokinetics of nasal nicotine delivery. Clin Pharmacokinet 31:65–80

Smith RE (2003) The cost of remembering to remember in event-based prospective memory: investigating the capacity demands of delayed intention performance. J Exper Psychol Learn Mem Cogn 29:347–361

Smith RE, Bayen UJ (2004) A multinomial model of event-based prospective memory. J Exper Psychol Learn Mem Cogn 30:756–777

Smith RE, Hunt RR, McVay JC, McConnell MD (2007) The cost of event-based prospective memory: salient target events. J Exper Psychol Learn Mem Cogn 33:734–746

Thayer RE (1989) The biopsychology of mood and arousal. Oxford University Press, New York

West RJ, Hack S (1991) Effects of cigarettes on memory search and subjective ratings. Pharmacol Biochem Behav 38:281

West RJ, Krompinger J, Bowry R (2005) Disruptions of preparatory attention contribute to failures of prospective memory. Psychon Bull Rev 12:502–507