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Effects of nicotine on visuospatial attentional orienting in non-smokers

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ABSTRACT

Nicotine is a highly addictive substance, suggested to be in part due to its cognitive enhancing effects in the attentional domain. Improvements in stimulus selection with nicotine have been reported but its effects on visual–spatial selective attention are unclear. This study utilized event-related potentials (ERPs) to examine the acute effects of nicotine on selective attention in non-smokers performing a Posner-type visuo-spatial task. The attentional processing of visual–spatial locations is reflected in the P1 ERP component, which represents earlier stages of visual analysis. 24 non-smokers received nicotine gum (6 mg) in a randomized, double-blind, placebo-controlled, repeated measures design. Behavioral performance and ERPs were assessed in response to target locations preceded by valid, invalid and neutral cues. Nicotine did not affect behavioral performance indices. P1 amplitudes were greater in valid and neutral cue trials compared to invalid cue trials and acute nicotine administration (vs. placebo) was found to increase P1 amplitudes in the right hemisphere, particularly in valid cue trials. In addition, in high symptomatic subjects (as indexed by greater increases in heart rate post-administration), nicotine (vs. placebo) produced greater P1 amplitudes in valid cue trials. The study concludes that nicotine enhanced visuo-spatial selective attention with regards to early visual encoding and analysis. These results demonstrate support in general for the attentional effects of nicotine and nicotinic agonists and they specifically extend these effects to include orienting of visual–spatial attention.

1. Introduction

Cognitive enhancement accompanying cigarette smoking is considered to be a motivational factor underlying the maintenance of smoking behavior in nicotine-dependent cigarette smokers (Evans and Drobes, 2009). Smoking has been shown to have beneficial effects on task performance as seen in psychomotor, vigilance and mnemonic tasks (Pritchard and Robinson, 1998; Heishman et al., 1994; Sherwood, 1993). Evidence from animal and human studies suggests that it is related to the central actions of nicotine, the main psychoactive ingredient in tobacco that is responsible for smoking reinforcement (Benowitz, 2008). Nicotine is known to stimulate brain nicotinic acetylcholinergic receptors (nAChRs), which have been implicated in a wide variety of behavioral and cognitive functions (Levin, 2002). Nicotine-induced performance enhancement has also been seen in nonsmokers (Heishman et al., 2010; Foulds et al., 1996) and the cognitively impaired (i.e. schizophrenia patients, Alzheimer's patients) under single dose conditions (Newhouse et al., 1990). Although the specific mechanisms underlying these performance enhancements seen with smoking/nicotine are not well understood, there is mounting evidence that the performance improvements may reflect the direct actions of nicotine on specific cognitive operations, particularly in the working memory and attentional domains (Newhouse et al., 2004), with the effects frequently being attributed to enhanced stimulus selection mechanisms occurring at early and/or late stages of the information processing chain (Kassel, 1997).

Selective attention allows for the processing of relevant stimuli and simultaneously inhibits the processing of irrelevant stimuli. Although behavioral studies have provided mixed support for nicotine's ability to modulate stimulus selection processes, findings of improved task performance with smoking/nicotine are frequently interpreted within the stimulus filter hypothesis, which suggests that nicotine facilitates task performance by acting as a selective stimulus-barrier, screening out irrelevant and distracting stimuli from the smoker's awareness and thereby freeing up resources that can be allocated to the focusing and extended processing of relevant stimuli, thus improving performance outcome (Kassel, 1997). These two processes, the "gating" out of irrelevant stimuli and the "gating in" of relevant stimuli, should not be mutually exclusive, but the existence of one does not necessarily ensure the presence of the other. Studies on the stimulus-filter-hypothesis, or more specifically on selective aspects of attention have been inconclusive (Kassel, 1997); however one recent study has shown evidence for a two-process model of visual–spatial selective attention, where one

Abbreviations: EEG, electroencephalogram; ERP, event-related potential; nAChRs, nicotinic acetylcholinergic receptors; HR, heart rate; bpm, beats per minute; HPR, high-pulse responder; LPR, low-pulse responder; RT, reaction time; ANOVA, analysis of variance.

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mechanism (facilitation) influences relevant stimuli and another (suppression) acts to filter distracting stimuli (Couperus and Mangun, 2010).

Visual spatial attention, the most studied variety of selective attention, has been investigated with spatial cueing (Posner-type) task paradigms, where cues provide information on the likely location of a subsequently presented target stimulus. Studies employing these visuo-spatial cueing tasks have typically focused on the validity effect i.e., the reaction time (RT) difference between validly and invalidly cued targets, which has been shown to decrease with systemic injection of nicotine in monkeys and rats and in non-deprived smokers following acute smoking (Witte et al., 1997; Phillips et al., 2000). The degree to which these behavioral improvements in attention reflect a true enhancement or a reversal of attentional impairment associated with smoking withdrawal in smokers is as yet unclear since one study in non-smokers did not find an influence of transdermal nicotine on the validity effect (Griesar et al., 2002) but another study did using relatively low (1 and 2 mg) nicotine gum dosages in non-smokers (Thiel et al., 2005). The behavioral effects of nicotine in these visuo-spatial cueing tasks suggest involvement of attentional operations specific to the processing of invalidly cued trials (Kastner and Ungerlerder, 2000; Motter, 2000). Posner's theory of attentional processing within this paradigm asserts that disengagement and shifting processes of visual spatial attention are required in invalid trials in order to reorient attention to valid locations (Posner and Petersen, 1990). It has been suggested that nicotine may facilitate these additional operations (i.e., disengagement of attention from the invalidly cued locations) in order to speed the reorienting of attention (Witte et al., 1997).

As electroencephalogram (EEG)-derived event-related potentials (ERPs) can be obtained non-invasively from individuals while performing cognitive tasks and have a high temporal resolution (1 ms), they have frequently been used as a tool to investigate and track time-dependant brain mechanisms involved in cognitive processing, allowing for the probing of early and late information stages that may be affected by attentional modulation. ERPs have been widely used to study the effects of visuospatial attention upon stimulus processing (see Hillyard and Anllo-Vento, 1998). In cued target detection tasks, the first attentional effects on target processing are manifest as amplitude modulations of early sensory-evoked components such as the P1, which has a positive polarity that occurs ~100 ms post stimulus and is maximal at posterior sites (Mangun and Hillyard, 1995). The visual P1 is generally thought to reflect activity of early perceptual processes, representing earlier stages of visual analysis (Luck and Girelli, 1998). In spatial cueing tasks, peak amplitudes of the P1 are larger for validly cued stimuli than for invalid ones (Mangun and Hillyard, 1995) and tend to be reduced on invalidly cued trials relative to neutral trials (i.e., trials with ambiguous cues). It has been suggested that the P1 component of the ERP reflects attentional suppression at uncued locations since this component differs between valid and invalid trials but not between valid and neutral trials (Meinke et al., 2006). Generators of the P1 have been localized in extrastriate cortex and are believed to be influenced by top-down activity originating in the frontal lobes (Heinze et al., 1994).

Using ERP measures, studies with both smokers and non-smokers have found nicotine to operate at multiple processing levels to affect stimulus input with P50, MMN, and P300 ERP components having indicated that nicotine increases the automatic 'gating in' of relevant sensory input and inhibits pre-attentive processing of redundant sensory information (Knott et al., 2009a, 2010a, 2010b, 2011), augments automatic stimulus sensory memory-based change detection (Inami et al., 2005; Fisher et al., 2010), reduces involuntary (exogenous) attentional switching to distractors (Knott et al., 2009b), and both guides and augments the effortful (endogenous) allocation of attentional resources to target-embedded attended stimuli (Knott et al., 1995, 1999; Pritchard et al., 2004; Shah et al., 2011). In visuo-spatial cueing tasks, it is possible that nicotine augments either the enhanced processing of validly (to-be-attended) cued locations, the suppressive processing of invalidly (to-be-ignored) cued locations, or both. In the first ERP study to assess the visuospatial attentional effect of nicotine in non-smokers, Meinke et al. (2006) reported that a relatively low dose of nicotine gum (2 mg) in non-smokers did reduce the behavioral validity effect but did not affect early (~100 ms) perceptual processes, as measured by P1 and N1 ERP components.

1.1. Objectives and hypotheses

As our previous work has reported nicotine-induced visual P1 amplitude increases in a non-cued selective attention task in non-smokers (Knott et al., 2009b), the goal of this study is to further explore nicotine-induced attentional alterations in non-smoker individuals and more specifically, to examine the effects of nicotine on visual selective attention in a spatial cueing paradigm. The study replicated Meinke et al.'s (2006) task methodology using their 'endogenous' spatial cueing paradigm, but administered a higher gum dose (6 mg vs. 2 mg) of nicotine. This higher dose of nicotine has been shown to enhance pre-attentive (Knott et al., 2009a, 2010a, 2010b, 2011; Inami et al., 2005; Fisher et al., 2010) and attention-dependant ERPs (Knott et al., 1995, 1999; Pritchard et al., 2004; Shah et al., 2011) in the auditory modality and may also elicit enhanced early visual processing not seen with smaller doses. As nicotine effects may well vary with its central bioavailability, comparisons were made between individuals exhibiting relative low and high nicotine-induced increases in heart rate, which have been shown to relate to nicotine dose (Heishman et al., 1993; Parrott and Hinder, 1989) and peak arterial nicotine concentrations (Armitage et al., 1978), with the latter coinciding with brain nicotine levels (Rose et al., 2010). In our recently published ERP study examining visuospatial selective attention, individual differences in nicotinic response, as measured by heart rate, were found to moderate N2pc, an ERP index of visual–spatial selection (Shah et al., 2011). Thus, in line with the contention that nicotine may differently modulate to-be-attended (i.e. validly cued) and to-be-ignored (invalidly cued) stimulus location, it was predicted that nicotine would result in improved behavioral performance indices of response accuracy and speed and would increase neural processing during cued target detection as reflected by enhanced P1 amplitudes in valid trials compared to invalid trials. In our earlier study of visual selective attention in a visual search paradigm, nicotine-enhanced selection varied with apparent bioavailability as indexed peripherally by pulse (heart) rate increases with nicotine (Shah et al., 2011), which have been shown to relate to nicotine dose (Heishman et al., 1993) and peak arterial nicotine concentration (Armitage et al., 1978). Accordingly, the predicted effects in the current study were expected to be observed more in high (vs. low) symptomatic (heart rate) responders to acute nicotine. As any evidence of nicotine-enhanced cognitive processing in smokers may be interpreted as a reversal of impairment associated with tobacco withdrawal, this investigation was carried out in non-smokers.

2. Experimental procedures

2.1. Participants

Twenty-four non-smoker (14 females) healthy, right-handed volunteers, aged 18–24 ($M = 21.88$, $SE \pm 3.11$) who had smoked fewer than 10 cigarettes in their lifetime and had not smoked any cigarettes within the past year were recruited into the study. Volunteers were medication free and reported negative psychiatric, neurological and alcohol and drug abuse histories. Written informed consent was obtained by the participants, approved by the Research Ethics Boards of the Royal Ottawa Health Care Group and the University of Ottawa.

2.2. Design

Volunteers participated in a randomized, double-blind, repeated-measures design, which involved two morning sessions (with at least

1 day apart). By random assignment, half received nicotine gum during the first session and a placebo gum in the second, while the remaining half received the gum treatments in reverse order.

2.3. Procedure

Upon arrival (9 a.m.), volunteers confirmed overnight abstinence from caffeine, nicotine and drugs. Following >75% response accuracy on the practice spatial cueing task, vital signs were taken and gum was administered with concurrent EEG hook-up. Vital signs were re-assessed immediately after gum administration completion and were followed by task presentation and then the completion of questionnaires assessing mood and adverse events.

2.4. Drug

A single dose of 6 mg of cinnamon-flavored nicotine gum (4 mg Nicorette Plus® + 2 mg Nicorette®) or commercially available cinnamon-flavored sugar-free gum (2 pieces), as placebo, was administered. By manufacturer suggestion, volunteers chewed twice every minute for 25 min. This was followed by the chewing of a strong mint gum for 2 min to eliminate perceived gustatory differences. Nicotine dose was expected to produce a blood nicotine level of 15–20 ng/ml, which approximates nicotine level reached with the smoking of one cigarette with a moderate nicotine yield (Hukkanen et al., 2005). Although commercial and nicotine gum pieces were virtually identical in size, shape and color, volunteers wore a blindfold and nose plug throughout the chewing periods to help disguise any gum differences.

2.5. Task

Participants were seated in a dimly lit and isolated chamber in front of a monitor, 100 cm in front of them. A select but identical version of the spatial cueing paradigm employed by Meinke et al (2006), using endogenous cues only, lasting approximately 45 min, consisted of presentation of visual stimuli (660 trials) divided in six experimental blocks (30 s breaks in between each block). Stimulus presentation was controlled by Presentation® software (http://nbs.neuro.bs.com) running on an IBM compatible computer. The displayed stimulus trials (Fig. 1) consisted of a diamond in the center of the screen and two empty, white rectangles on each side of the diamond. This display was shown continuously on the monitor. The participant was instructed to remain focused on the central diamond during the task paradigm. On each trial, a 'go'-target stimulus, which was a black circle, or a 'nogo'-target stimulus, which was a black diamond, appeared within the rectangles. The target (go) and non-target (nogo) stimuli were presented for 50 ms and participants were instructed to respond to the circles (go trials) by pressing a key pad with their dominant index finger as fast as possible and not to respond to the diamonds (nogo trials). Endogenous cues, consisting of sides of the central diamond lighting up for 50 ms, were presented prior to each target/non-target. The cue-target offset-to-onset interstimulus interval (CT-ISI) varied between 400 ms and 500 ms and the inter-trial interval (ITI; target offset to cue onset) varied between 1000 and 1100 ms. Among the 660 cued trials, 110 were neutral, 110 were invalid and 440 were valid. A valid trial occurred when the target appeared at the pre-cued location, invalid trials occurred when the target appeared at the uncued location and neutral trials occurred when both sides of the central diamond lit up, thus providing no information about the probable location of the subsequent target. For each trial category, 75% were nogo-trials and 25% were go trials. Behavioral measures included percentage of correct responses and reaction times.

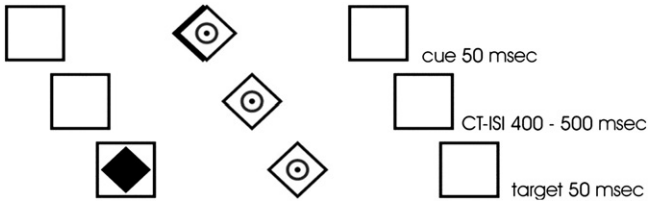

Fig. 1. Spatial cueing paradigm depicting an endogenous valid cue during a no-go (non-target) trial.

2.6. Ratings

To measure possible nicotine-modulated mood effect, mood was assessed post-gum administration and task completion using the Bond and Lader (1974) self-report questionnaire which consisted of sixteen 100 mm bipolar analogue scales (e.g. alert–drowsy, attentive–dreaming) and yielded 3 mood factors: alertness, contentedness, and calmness. Possible nicotine-related adverse events were assessed using Harkrider and Hedrick's symptom scales (2005) which were scored on a scale from 1 ("No symptoms at all") to 5 ("Severe symptoms," i.e., jittery, pounding headache, nausea.)

2.7. Vitals

Systolic (SBP) and diastolic (DBP) blood pressure (mm Hg) and heart rate (HR: beats per minute [bpm]) were measured before and after treatment, while participants were seated and resting.

2.8. ERPs

ERPs were recorded with $Ag^{+}/Ag^{+}Cl^{-}$ electrodes from 32 scalp sites placed according to the 10–10 recording system, using electronically linked mastoids as a reference and AFz as the ground. Electrodes were placed above and below the right eye and on the external canthi of both eyes to monitor vertical and horizontal electro-oculographic activity. Electrode impedances were kept below 5 kΩ and, using Brain Vision® Quickamp amplifier and Recorder software, amplifier filters and digitization rate were kept at 0.1–55 Hz and 500 Hz, respectively. EEG data was analyzed with Brain Vision® Analyzer (Brain Products, Germany) software. Digitally filtered (0.1–30 Hz), ocular corrected (Gratton et al., 1983) EEG epochs of 500 ms duration (beginning 100 ms pre-stimulus) with voltages <100 μV were averaged separately for all cue conditions.

The P1 component is maximal at posterior electrode locations and assessment of its amplitude was limited to left (P7) and right (P8) posterior hemisphere sites. Based on visualization of the grand average waveforms of this study and from Meinke et al. (2006), the P1 was assessed as the mean voltage (relative to pre-stimulus baseline) in the 90–150 ms interval, as shown in Fig. 2.

2.9. Statistics

Separate analysis of variance (ANOVA) procedures were used to analyze behavioral performance indices, P1 amplitudes, mood ratings and vital signs. To derive sub-groups based on physiological change, heart rate (HR) was expressed as a difference score (post-nicotine value minus pre-nicotine value) and a median split was employed to stratify the sample into two groups: high pulse responders (HPR [HR change of ≥0.5 bpm, average HR change = 5.67 bpm]) vs. low pulse responders (LPR [HR change of ≤.05 bpm, average HR change = −4.83 bpm]). The performance data was analyzed from go trials in a 2 (drug: nicotine and placebo), 3 (cue: neutral, invalid and valid) and 2 (stimulus field: left and right) ANOVA, with group as a between-subjects factor for % hits and reaction time (RT), respectively. In addition, an index of the 'validity effect' was constructed with reaction time (invalid scores minus valid scores) and analyzed with similar ANOVAs without the cue factor. As this study was centered on perception-related processing, ERP analysis was limited to nogo

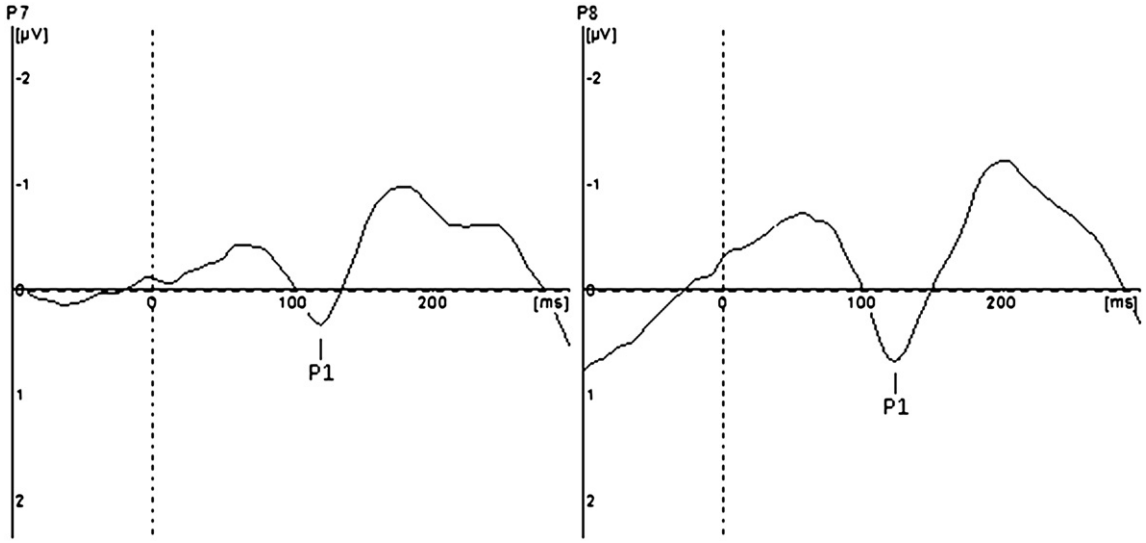

Fig. 2. Grand averaged waveforms at P7 and P8 (collapsed across cue, drug, group and laterality factors) displaying P1 time window.

trials. The P1 amplitudes were analyzed in a 2 (drug: nicotine and placebo), 3 (cue: neutral, invalid and valid), 2 (hemisphere: left and right) and 2 (laterality: ipsilateral and contralateral) ANOVA, with group as a between subjects factor. Ratings were analyzed with drug as a within-group factor and group as a between-group factor. Vital signs were analyzed by 2 (time: pre drug and post drug) and 2 (drug: nicotine and placebo) ANOVA. Greenhouse–Geisser corrections were applied where appropriate and significant effects ($p < .05$) as well as planned comparisons were followed up with Bonferroni-adjusted pairwise comparisons.

3. Results

3.1. Performance measures

Mean reaction times and percent hits are summarized in Table 1. No main effects of drug, group or cue were observed for percent hits. Reaction time analysis revealed no significant drug, group or cue main effects. A main effect of stimulus field on reaction time, $F(1,22) = 4.68$, $p < .05$, was revealed, which showed that right target field stimuli elicited a faster reaction time than left target field stimuli. Also, a planned pairwise comparison of target field × cue revealed a non-significant trend, $p = .08$, with neutral cues ($M = 475.20$ ms, $SE \pm 6.58$) displaying shorter reaction times than invalid cues ($M = 480.68$ ms, $SE \pm 7.99$) in the right stimulus field. The validity effect analysis also did not demonstrate any significant drug or group effects.

3.2. Ratings

Mood rating analysis demonstrated a significant main effect of group for contentedness, $F(1,22) = 7.82$, $p < .05$, where high pulse responders reported greater contentedness ($M = 6.70$, $SE \pm .30$) compared to low-responsive individuals ($M = 5.52$, $SE \pm .30$). No significant effects of drug or group were observed for alertness or calmness dimensions. Adverse events were affected, $F(1,23) = 4.39$, $p < .05$, by nicotine ($M = 1.58$, $SE \pm .17$), with greater symptom severity compared to placebo ($M = 1.17$, $SE \pm .10$). There were no group differences for adverse events.

Table 1
Mean ($\pm SE$) percent hits and reaction times (ms) for valid, neutral and invalid cue trials during placebo and nicotine conditions.

Drug	Performance	Valid cue		Neutral cue		Invalid cue	
		Mean	*SE*	Mean	*SE*	Mean	*SE*
Placebo	% Hits	96.57	±0.65	97.50	±0.77	96.79	±0.76
	Reaction time	481.24	±7.80	482.16	±7.55	481.24	±7.51
Nicotine	% Hits	94.97	±0.83	96.36	±1.08	95.15	±1.72
	Reaction time	484.37	±7.51	481.70	±6.49	482.86	±7.46

3.3. Vital signs

There was a main effect of drug on heart rate (HR), $F(1,23) = 5.07$, $p < .05$, with nicotine ($M = 69.38$ bpm, $SE \pm 1.64$) demonstrating greater beats per minute compared to placebo ($M = 66.04$ bpm, $SE \pm 1.64$). Planned pairwise comparison revealed a significant difference between post-nicotine administration and drug, ($p < .05$), with nicotine ($M = 69.58$ bpm, $SE \pm 1.68$) showing a greater effect than placebo ($M = 66.21$ bpm, $SE \pm .1.74$). There was no significant difference in HR values between nicotine and placebo sessions pre-gum administration. There were no significant drug effects for DBP or SBP.

3.4. P1 amplitudes

No main effects were observed for cue condition but follow-up of a cue × laterality interaction, $F(2,44) = 5.70$, $p < .02$, found that valid cues ($M = 1.38$ μV, $SE \pm .25$) elicited greater, $p < .05$, P1 amplitudes than invalid cues ($M = .83$ μV, $SE \pm .37$) and invalid cues also elicited reduced, $p < .03$, amplitudes compared to neutral cues ($M = 1.50$ μV, $SE \pm .25$) at sites ipsilateral to the target. Additionally, follow-up of a significant cue × hemisphere interaction, $F(2,44) = 4.17$, $p < .02$, revealed a significantly greater, $p < .05$, P1 elicited by valid cues compared to invalid cues and also greater, $p < .05$, P1 amplitudes were seen with neutral cues compared to invalid cues in the right hemisphere (Fig. 3).

No main effects of drug were observed, but a follow-up of a significant drug × hemisphere interaction, $F(1,22) = 7.01$, $p < .01$, revealed a non-significant trend, $p = .065$, with nicotine ($M = .81$ μV, $SE \pm .28$) producing greater P1 amplitudes than placebo ($M = .54$ μV, $SE \pm .28$) in the right hemisphere. A significant 4-way interaction between drug × cue × group × hemisphere, $F(2,44) = 4.36$, $p < .03$, was also seen. Follow-up pairwise comparisons revealed a greater, $p < .05$, P1 amplitude during the nicotine condition ($M = .96$ μV, $SE \pm .36$) compared to placebo ($M = .44$ μV, $SE \pm .40$) specifically in high pulse responders (HPRs) in valid cue trials at right hemisphere sites (Fig. 4).

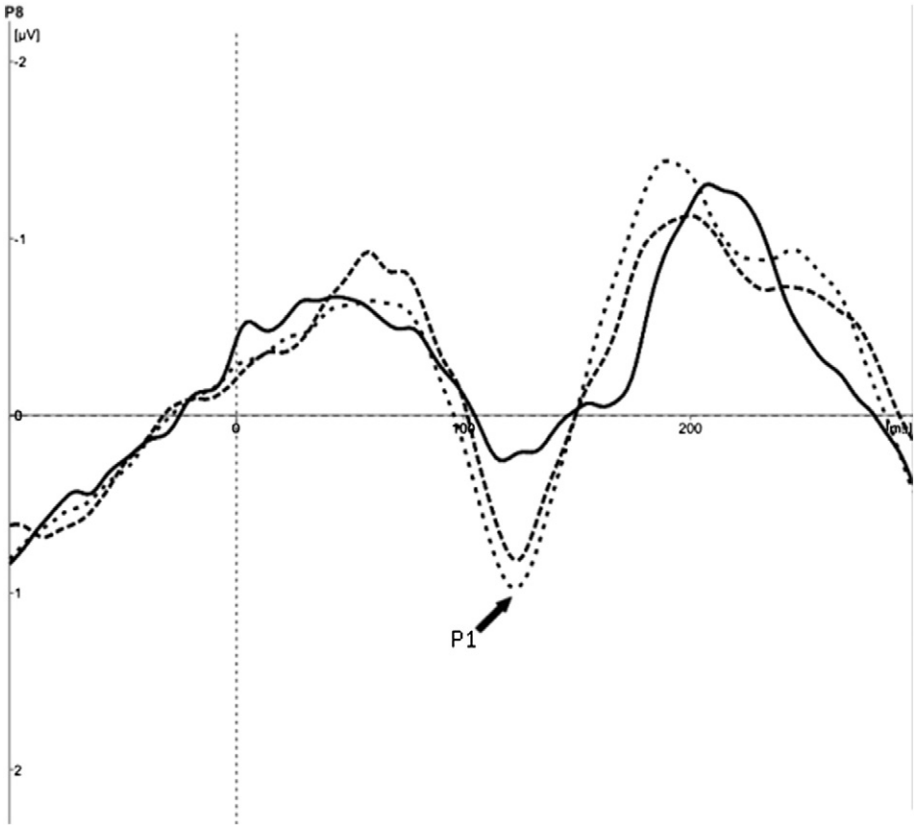

Fig. 3. Grand averaged P1 amplitudes (collapsed across drug, group and laterality) in the right hemisphere displaying significantly reduced, $p < .05$, invalid trials (solid line) compared to neutral trials (dashed line) and valid trials (dotted line), respectively.

4. Discussion

This study investigated the acute effects of nicotine on behavioral and electrophysiological indicators of visually cued target detection in non-smoker groups that differed in their somatic responsiveness to nicotine. The P1 ERP was assessed during a Posner-type spatial cueing task (Meinke et al., 2006) designed to elucidate neural mechanism underlying the putative attentional enhancing properties of nicotine. In go (target) trials, similar behavioral responses were seen for each cue type and in both nicotine and placebo conditions, including percentage of hits, misses and reaction time. Nicotine also did not alter the validity effect (i.e. the reaction time difference between validly cued trials and invalidly cued trials), contrary to the hypotheses of the study. However, at the electrophysiological level, in no-go trials, P1 amplitudes were greater in valid and neutral trials compared to invalid trials. Acute nicotine administration was found to selectively enhance P1 amplitudes in valid cue trials, the effect lateralized to the right hemisphere. Comparing subgroups differing in somatic responsiveness to nicotine, it was the high symptomatic subjects (as indexed by greater increases in heart rate post-administration) who produced greater P1 amplitudes in valid cue trials during nicotine administration compared to placebo. These ERP findings provide some tentative support for the hypothesis that nicotine improves visuospatial selective attention and they have implications for the stimulus filter hypothesis of smoking/nicotine-enhanced cognition.

4.1. Behavioral effects of nicotine

Contrary to our hypotheses and the visual cueing literature, nicotine did not exert an effect on response accuracy or response speed measures of behavioral performance. Many studies have reported increased target detection accuracy and improved reaction times with both acute smoking and nicotine administration in smokers during varied visual attention tasks including visual cueing paradigms (Witte et al., 1997; Murphy and Klein, 1998). Studies using an abstinent smoking population find more reliable behavioral results; however, this may be due to withdrawal-induced performance impairments returning to normal levels (Heishman et al., 1994). Similar results have also been observed with non-smokers (Thiel et al., 2005; Meinke et al., 2006), however not all studies have found nicotine-enhanced behavioral performance in non-smokers (Shah et al., 2011; Griesar

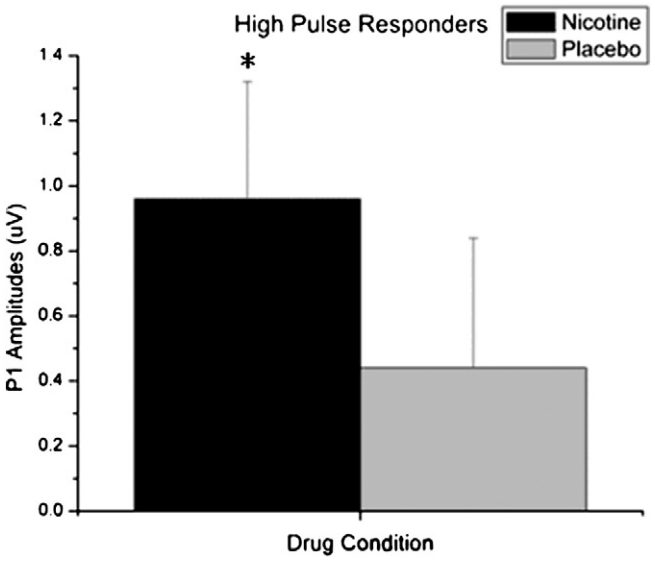

Fig. 4. Grand averaged P1 amplitudes (collapsed across laterality) in the right hemisphere during valid cue trials showing significantly greater response, $p < .05$, in nicotine (black) vs. placebo (grey) conditions for HPRs. These differences were not found with LPRs.

et al., 2002). Griesar et al. investigated the effect of nicotine in an endogenously cued target detection task and did not find any beneficial effects of nicotine on invalidly cued trials in non-smoking subjects. The lack of effects of nicotine on behavioral performance corresponds with a number of previous studies that assessed these effects in non-smokers (Newhouse, Potter and Singh, 2004). It is suggested from these performance data that non- or never smokers may be already operating at or near their optimal level of performance due to nicotinic receptor mechanisms underlying behavioral responses being maximally activated in this group and that increased nicotinic stimulation may not produce corresponding functional improvements in this non-smoker group (Newhouse, Potter and Singh, 2004).

If non-smoker individuals are already performing at optimal levels, this also has implications for nicotine's ability to impact performance. The current paradigm was similar to that employed by Meinke et al. (2006) who observed a strong cue validity effect and its reduction by a relatively small nicotine dose. However, the validity effect in the current study was not present and behavioral nicotine effects were absent. In the Meinke et al. study, two different cue paradigms (endogenous and exogenous) were randomly intermixed within the spatial cueing task. These additions could have made the task longer and more difficult for the participants, causing greater fatigue and resource utilization, which perhaps set the stage for a greater validity effect and its reversal by nicotine in non-smokers. In future studies, a more complex or difficult task may result in more effective manipulation of reaction time and/or accuracy, as the spatial cueing paradigm is a relatively easy task, with most participants achieving at least 75% accuracy on their first practice.

Differences in behavioral results could also be due to the nicotine dose. Both this study, which used 6 mg Nicorette gum, and the study by Griesar et al. (2002), which used a 7 mg transdermal patch in their "low" nicotine condition and two 7 mg transdermal patches in their "high" nicotine condition, did not find a reduced reaction time difference between validly and invalidly cued targets with nicotine administration. This is compared to studies using much smaller doses, 2 mg of Nicorette gum (Meinke et al., 2006). Our higher nicotine dose could explain the increase in reported adverse nicotine-related symptoms found in this study (but not in the Meinke et al., study), which may have in turn deleteriously affected performance. It is suggested that future studies assess nicotine-modulation of visual spatial behavioral response using multiple doses to better control the amount of nicotine exposure.

4.2. Electrophysiological effects of nicotine

The spatial cueing paradigm was effective in eliciting the characteristic P1, which has a positive polarity that occurs ~100 ms post stimulus and is maximal at posterior sites. The visual P1 is generally thought to reflect activity of early perceptual processes, representing earlier stages of visual analysis. In the current spatial cueing task, peak amplitudes of the P1 were larger for both validly cued stimuli and neutral cues than for invalid ones. These findings are in agreement with the visual selective attention literature, which has shown that P1 is attenuated during invalidly cued target detection trials (Mangun and Hillyard, 1995). These findings also show support for the P1 ERP reflecting attentional suppression at uncued locations (Luck, 1995; Meinke et al., 2006), since this component differs between valid and invalid trials but not between valid and neutral trials. Our findings also reinforce the idea of a frequently observed right-hemispheric dominance for spatial attentional representation in the brain, which has been evidenced with lesion studies (Weintraub and Mesulam, 1987) and ERP studies (Miniussi et al., 2002) of spatial attention.

Acute nicotine administration was found to increase P1 amplitudes as compared to placebo in the right hemisphere. This nicotine-enhancing effect was seen specifically in validly cued trials compared to neutral or invalid trials, thus supporting the hypothesis, at least at the neural level, that early visual spatial attention was enhanced by nicotine. Moreover, when assessing subjects stratified by physiological (HR) response to nicotine, this effect was seen specifically in high pulse responders, with nicotine (vs. placebo) producing greater P1 amplitudes in validly cued trials in the right hemisphere, thus supporting the hypothesis that enhanced neural processing by nicotine is observed more in high (compared to low) symptomatic responders (Shah et al., 2011). Together, these results show that acute nicotine seems to augment the enhanced processing of validly (to-be-attended) cued locations, this effect being observed in high (vs. low) symptomatic responders. As nicotine was administered to non-smokers, the study outcomes likely reflect the absolute enhancing effects of nicotine and do not reflect relief from, or normalization of, withdrawal-associated performance decrements that may be observed with tobacco abstinent smokers.

These ERP results offer partial support of the stimulus-filter hypothesis. We suggest that in line with the hypothesis, nicotine narrowed early visual–spatial attentional focus, augmenting attention to relevant/significant stimuli (in this case valid cues). However, the hypothesis also stipulates that the allocation of attentional resources to the processing of irrelevant or distracting stimuli (in this case invalid cues) would be reduced. Although this dampening effect was seen in P1 amplitudes when amplitudes were collapsed across drug condition (with attenuated P1 for invalidly cued trials compared to valid and neutral cues), this effect was not seen with nicotine. In the current study, nicotine only modulated P1 amplitudes for validly cued trials. Moreover, this enhanced allocation of attentional resources did not lead to performance improvements, which is the expected behavioral result of the stimulus-filter hypothesis. However, many studies have now shown enhanced fMRI-BOLD (Giessing et al., 2006) and ERP response, including the visual P1 and the N2pc, without a similar increase in behavioral performance (Knott et al., 2009a; Shah et al., 2011). It is argued that EEG and ERP measures can provide information about the neurocognitive operations that cannot always be inferred from task performance measures. In contrast, the study from Meinke et al (2006) did not find modulation of early ERP components, even though they found a reduced validity effect with nicotine. It is probable that the higher dose of nicotine used in this study, as well as the modified task to focus on endogenous spatial cues (as opposed to both endogenous and exogenous cues), allowed for enhancement of the P1 component in this study, without any corresponding effect on behavioral performance.

There are a number of limitations in the study that temper the study findings. According to Evans and Drobes (2009), easy to perform tasks may sometimes fail to detect nicotine effects and so by incorporating a task with multiple difficulty levels, one can better assay the effects of nicotine. As mentioned, the difficulty level of the current task could be increased by including exogenous cues. Also, there was a lack of adjustment made to nicotine dosage based on participant body weight, as well as neglecting to account for individual differences in nicotinic absorption by analyzing blood samples of nicotine levels, which are variable in each person. This also has implications for our subgroups, as high and low responders were stratified based on heart rate, which is an indirect measure of nicotine absorption (Heishman et al., 1993; Parrott and Winder, 1989; Armitage et al., 1978). The lack of blood nicotine levels, as well as the lack of biochemical confirmation of abstinence from caffeine, alcohol, and drugs, remain a limitation of this study. In the future, the use of a nasal spray vehicle instead of gum may also prove to be a more effective route of administration, as a nasal spray more closely resembles the rapid absorbance seen with smoke inhalation (Lerman and Niaura, 2002). Finally, our ERP measures were extracted from posterior scalp regions and as attentional engagement in this paradigm has been associated with neural activation in visual, prefrontal and parietal cortices (Gunduz et al., 2011), not all relevant nicotine effects will have been captured with this approach.

5. Conclusions

In summary, several models of nAChR function, as well as data from other ERP studies, would have predicted a modulation of early

sensory components such as the P1; however enhancement of this component was not seen in a previous study using a small dose of nicotine in non-smokers (Meinke et al., 2006). In the current study, P1 amplitudes, when collapsed across drug condition, were significantly enhanced in validly (endogenous) cued trials compared to invalidly cued trials, but not neutral trials, in a spatial cueing task, which supports the notion that P1 reflects attentional suppression at uncued locations. However, a moderate dose of nicotine (6 mg) was shown to enhance P1 for validly cued trials only, specifically in symptomatic responders, which shows support for a second attentional enhancing mechanism which enhances selective attention for relevant stimuli as opposed to suppression of irrelevant stimuli. The study concludes that nicotine enhances selective attention with regards to early visual encoding and analysis and these results demonstrate support for nicotine-related cognitive enhancement that could explain, in part, motivation for tobacco dependence.

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