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# Neural effects of acute nicotinic treatment on visual spatial attention in non-smokers

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ABSTRACT

Enhanced cortical cholinergic signaling associated with nicotinic acetylcholine receptor (nAChR) stimulation has been linked with pro-cognitive actions in a variety of performance domains, including attentional tasks. Improvements in stimulus selection with the nAChR agonist nicotine have been reported but its effects on visual spatial selective attention are unclear. Employing a double-blind, placebo-controlled design, this study examined the acute actions of nicotine (6 mg) in 24 non-smokers performing a visual search task of spatial attention that was probed with behavioral performance measures and the N2pc component of the event-related potentials (ERPs), which served as a neural index of spatial attentional selection. Nicotine did not affect behavioral performance indices. In high symptomatic subjects (as indexed by greater increases in heart rate post-administration), nicotine was associated with an N2pc amplitude enhancement while in low symptomatic individuals it was associated with an N2pc difference amplitude decrease. Nicotine modulation of the ERP marker of spatial attentional selection corroborates in general the attentional effects of nAChR agonists and extends these properties to include altered selective mechanisms during visual spatial processing.



## 1. Introduction

### 1.1. Acetylcholine and cognition

Electrophysiological and behavioral studies on the role of acetylcholine in cognition have implicated cortical cholinergic inputs in the detection and selection of stimuli for extended processing and in the allocation of appropriate processing resources to these functions (Sarter and Bruno, 1997). Beyond its putative role as a slowly acting neuromodulator that has been posited to influence performance via diffuse arousal regulation, cholinergic activity manifesting on multiple timescales (seconds, tens of seconds, and minutes) supports and is necessary for the mediation of defined cognitive operations (Parikh and Sarter, 2008). This mediation occurs as a result of optimizing the signal-driven (bottom-up effects), and cognitive modulation (top-down effects) of detection of behaviorally relevant stimuli in attention-demanding contexts (Sarter et al., 2005). Under taxing attentional conditions involving performance decrements in response to detrimental challenges (e.g. changing target stimulus characteristics, presentation of distractors, prolonged time-on-task), motivated attentional systems are recruited via cholinergic activation both of the 'anterior attentional system', which mediates the knowledge-driven detection and selection of target stimuli (including the filtering of noise and distractors), as well as sensory and posterior cortical regions to modify receptor field properties or the suppression of contextual information (Sarter et al., 2001, 2006).

In previous human and animal studies of cognition, the nicotinic acetylcholine receptor (nAChR) system has been extensively implicated with the pro-cognitive effects of nAChR agonists, being linked to attentional improvements, in particular under high attentional demand (Howe et al., 2010; Leiser et al., 2009; Mansvelder et al., 2006; Poorthuis et al., 2009; Sarter et al., 2009). In a recent meta-analysis, significant positive effects of nicotine on performance were observed in six domains: fine motor, alerting attention–accuracy and response time, orienting attention, reaction time, short-term episodic memory-accuracy, and working memory-reaction time (Heishman et al., 2010). As these effects were seen in non-smokers or smokers who were not tobacco deprived, this likely represents a true performance enhancement not confounded by withdrawal relief. Nicotine, the prototypical nAChR agonist, has been shown to enhance several aspects of visual attention in non-smokers as well, including sustained attention, attentional span and attentional shifting, spatial attention, and visuospatial reorienting (Barr et al., 2008; Griesar et al., 2001; Le Houezec et al., 1994; Poltavski and Petros, 2006; Vossel et al., 2008), with the beneficial effects frequently being attributed to enhanced stimulus selection mechanisms occurring at early and/or late stages in the information processing chain (Kassel, 1997). Overall, nicotine has found to influence sensory, motor, attentional, executive, learning

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and memory domains (Kassel, 1997; Stolerman et al., 2000; Rezvani and Levin, 2003). The high temporal resolution (on the order of milliseconds) afforded by the event-related potentials (ERPs) probing of these processing stages in non-smokers and smokers has found nicotine to operate at multiple processing levels to affect stimulus input (Knott, 1978; Knott et al., 2009), with P50, P300a, MMN, Nd and P300b ERP components having indicated that nicotine inhibits the pre-attentive processing of redundant sensory information (Knott et al., 2010a,b), reduces involuntary (exogenous) attentional switching to distractors (Knott et al., 2009), increases the automatic 'gating in' of relevant sensory input (Baldeweg et al., 2006; Engeland et al., 2002; Fisher et al., 2010; Harkrider and Hedrick, 2005; Inami et al., 2005; Martin et al., 2009), and both guides and augments the effortful (endogenous) allocation of attentional resources to target-embedded attended channels (Knott et al., 1995, 1999, 2006; Pritchard et al., 2004), respectively.

### 1.2. Nicotine and spatial attention

Nicotine's effects on the spatial focus of attention have been less explored. Many of the basic properties of visual selective attention have been studied mainly through the use of the visual search paradigm, in which participants must search for a designated target in an array of distractors and are required to indicate whether the target is present or absent in each search array. Many studies have found that mechanisms of visual spatial attention are integral to visual search and contribute to the level of performance during the task, including mechanisms of attentional suppression (of unattended inputs) and attentional facilitation (of attended inputs) (Hillyard and Anllo-Vento, 1998; Hillyard et al., 1998; Luck, 1994, 1995).

### 1.3. N2pc ERP component

ERP studies on visual selective attention in visual search paradigms have focused on the N2pc component (Luck and Hillyard, 1994a, 1994b), which has a negative polarity that occurs at a latency of 200–300 ms and is observed at the posterior sites in the hemisphere contralateral to the position of the target stimulus. N2pc has been suggested to be present for both targets and non-targets that require careful distinguishing and to be absent when non-targets can be distinguished easily with one feature or if there is an absence of distractor stimuli surrounding the target (Girelli and Luck, 1997). Although the component was initially conceived as an attentional process suppressing irrelevant information from distractor items, it has recently been interpreted as an index of visual spatial shifts of attention to the location of the target (Lorenzo-López et al., 2008).

Visual search studies in smokers have shown that abstinent smokers had faster response latency after nicotine (versus placebo) without a corresponding loss in response accuracy, which indicates a better focusing of attention on task relevant items (Rycroft et al., 2005). These effects however may reflect a normalization of impacted search processes resulting from smoking abstinence and not a true enhancement of visual search per se.

### 1.4. Objectives and hypothesis

Evidence gleaned from genetic strategies and from neuropsychiatric patients has suggested that cholinergic mechanisms, and nAChR mechanisms in particular, may provide a selective contribution to the modulation of the spatial scale of visual attention (Greenwood et al., 2005; Levy et al., 2000). In this study, changes in visual search performance resulting from nAChR stimulation with acute nicotine administration in non-smokers were studied along with N2pc, which served as neural probe for bridging the gap between receptor and behavior. 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) and peak arterial nicotine concentrations (Armitage et al., 1978), with the latter coinciding with brain nicotine concentrations (Rose et al., 2010). It was predicted that nicotine would result in improved behavioral performance indices of response accuracy and speed and would increase neural processing during visual search as reflected by enhanced N2pc amplitudes, both effects being expected to be observed more in high (vs. low) symptomatic (heart rate) responders.

## 2. Methods

### 2.1. Participants

Twenty-four non-smoker (14 females), healthy, right-handed volunteers (M = 21.88 yrs [*SE* = 3.11]) who had smoked fewer than 10 cigarettes in their lifetime and not smoked any cigarettes within the past year were recruited into the study. Volunteers were free of medication (with the exception of oral contraceptive pill), and had a negative self-reported psychiatric, neurological and alcohol or substance abuse history. Participants were divided into sub-groups based on heart rate measures. To derive sub-groups, heart rate measure was expressed as a difference score (post-placebo/nicotine value minus pre-placebo/nicotine value) and a median split was employed on the difference outcome values to stratify the sample into two groups: high pulse responders (HPR [HR change of $\geq$0.5 bpm]) versus low pulse responders (LPR [HR change of $\leq$.05 bpm]). The heart rate change scores of the HPR group ranged from 1 to 21 bpm and exhibited a mean of 5.67 bpm, while heart rate change in the LPR group ranged from −13 to 0 bpm, with a mean of −4.83. Independent sample *t*-test scores revealed no significant (>.05) difference between LPR and HPR groups with respect to age, baseline pulse, baseline systolic blood pressure and baseline diastolic blood pressure. Participants gave written informed consent, as 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, placebo-controlled, repeated-measure design, which involved two morning sessions at least one day apart (range = 2–7 days). Half of the participants (randomly selected) received placebo gum during their first session and nicotine gum during their second session, while the remaining half received placebo and nicotine treatments in reverse order.

### 2.3. Procedure

Upon arrival at the laboratory (8:00 a.m.) participants verbally confirmed their overnight abstinence from caffeine, nicotine, alcohol, drugs, and medications. After achieving >75% response accuracy on the practice visual search task, vital signs were taken and drug treatment was administered, while ERP recording electrodes were attached. Vital signs were taken again after completion of treatment administration, after which the visual search task was presented. At the end of the task, participants completed mood and adverse events questionnaires.

### 2.4. Nicotine administration

Two pieces of cinnamon-flavored nicotine polacrilex (6 mg [4 mg Nicorette Plus®, 2 mg Nicorette®]) or two commercially available cinnamon flavored sugar-free gum pieces, as placebo, were administered. As suggested by manufacturers, participants, with blindfold

and nose plug on, chewed twice every minute for 25 min and between bite times, parked gum between teeth and cheek followed by 2 min of chewing of a strong commercial mint gum to reduce gustatory sensations. The 6 mg dose of nicotine gum was expected to produce a blood nicotine level of 15–20 ng/ml, which approximates nicotine levels (15–30 ng/ml) reached with the smoking of a single cigarette (Hukkanen et al., 2005).

### 2.5. Visual search task

The visual search task has been adopted from the recent paper by Lorenzo-López et al. (2008). In short, the task involved six blocks of 250 trial presentations of eight bars (4 bars on the right and left hemifield). Three different trial types were randomly presented: homogeneous arrays (HA; $p=0.6$), arrays with a singleton pop-out orientation target (TA; $p=0.2$) defined by orientation, and arrays with a singleton pop-out color non-target (irrelevant distractor: DA; $p=0.2$) defined by color. HAs consisted of eight blue horizontal bars, TAs consisted of one blue vertical bar among seven blue horizontal bars, and DAs had seven blue horizontal bars and one red horizontal bar. Fig. 1 illustrates the visual search paradigm showing HA, DA and TA. Both TA and DA trials were equally likely to appear in the right or left visual field and their location was unpredictable. For further detail on the task please refer to Lorenzo-López et al. (2008). Participants were instructed to perform a visual search, which consisted of detecting a target stimulus (vertical bar) among an array of distractors by indicating whether the target was present or absent in each search array by pressing a green button on their response pad with one hand and a red button with the other hand, respectively, while fixating on a central cross between array presentations. Response buttons were counterbalanced across subjects. Behavioral measures included the number of correct responses (hits; expressed as % values), and the reaction times (RTs) of correct responses.

### 2.6. ERP recordings and N2pc amplitude measurement

Using the left and right mastoids as references and a ground electrode positioned between Fpz and Fz sites, ERPs were recorded with $Ag^{+}/Ag^{+}Cl^{-}$ electrodes from 32 scalp sites (10–10 recording system). Bipolar pairs of electrodes positioned at the external ocular canthi and above and below the right eye were used to record horizontal (HEOG) and vertical (VEOG) electrooculogram, respectively. All electrode impedances were kept below 5 kΩ and electrical activity was recorded continuously with an analog-to-digital sampling rate of 500 Hz, using an amplifier filter of 0.1–55 Hz. EEG data were analyzed with Brain Vision Analyzer (Brain Products, Germany) Software. Digitally filtered (0.1–30 Hz), EOG corrected EEG epochs of 500 ms duration (beginning 100 ms pre-stimulus) with voltages <100 μV were averaged separately for TAs, and DAs occurring in the right (RVF) and left (LVF) visual fields and for HAs (Woestenburg et al., 1983).

Measurement of N2pc amplitudes for TAs and DAs, typically shown to be maximal at posterior electrode locations, was limited to left and right hemisphere posterior electrode locations at parietal (P3/P4), occipital (O1/O2), and temporo-parietal (P7/P8) recording regions. The N2 posterior component mean amplitude was measured (relative to pre-stimulus baseline) in the latency window of 200–275 ms based on where the component appeared in the grand mean waveforms of the present study and also from data collected in young adults by Lorenzo-López et al. (2008). N2pc was also measured from difference waveforms, which involved the point-by-point digital subtraction of waveforms containing an ipsilateral target (relative to the electrode location) from those waveforms containing a contralateral target.

### 2.7. Self-report measurement of mood state and adverse physical symptoms

The Bond and Lader (1974) questionnaire and adverse events scale (Harkrider and Hedrick, 2005) were administered to assess mood states and adverse events, respectively. The adverse symptoms scale was administered to rate the degree of physical symptoms, which were scored on a scale from 1 ("No symptoms at all") to 5 ("Severe symptoms," i.e., jittery, dull/pounding headache, nausea, vomiting.)

### 2.8. Vital signs measurement

Systolic blood pressure (SBP), diastolic blood pressure (DBP: milliliters per milligram of mercury [mm/mg Hg]) and heart rate (HR: beats per minute [bpm]) were measured before and after treatment administration, while participants were semi-reclined and resting.

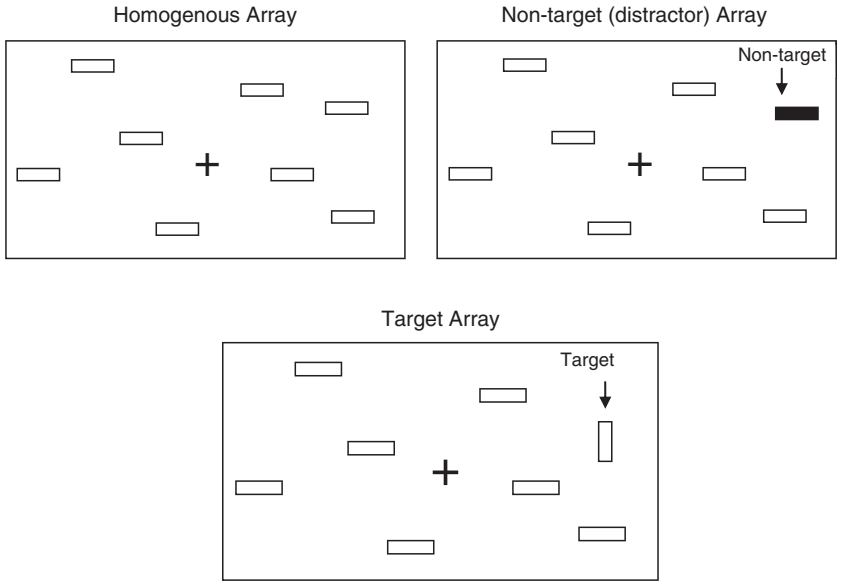


**Fig. 1.** Schematic of visual search paradigm showing homogeneous (HA), color non-target (DA) and target arrays (TA).

### 2.9. Statistics

Separate mixed analysis of variances (ANOVA) with between-group and within-group factors was carried out to analyze behavioral performance, self-report measures, vital signs, and N2pc amplitudes. For performance measures, the within-group factors included drug and array type (HA, TA, DA), while for self-report measure drug was the only within-group factor. Vital signs were analyzed by 2 (time: pre drug and post drug)×2 (drug: nicotine and placebo) ANOVA. The TA and DA N2pc amplitudes were analyzed by separate 2 (group: responsive and nonresponsive), 2 (drug: nicotine and placebo), 2 (stimulus field: right and left visual field), 2 (laterality: ipsilateral and contralateral) and 3 (region: parietal P3/P4, occipital O1/O2 and temporo-parietal T5/T6) ANOVAs. Greenhouse–Geisser corrections were applied when appropriate. Pairwise comparisons followed all significant ($p<.05$) interactions and main effects and were Bonferroni adjusted.

## 3. Results

### 3.1. Performance measures

Table 1 summarizes the mean percent hits and RTs for performance measures. No main effects of drug or group were observed on percent hits. A main effect of array type on percent hits ($F$ [2, 44] = 17.79, $p<.001$) was however revealed. A follow-up pairwise comparison showed a reduced performance level for TAs than that for HAs ($p<.001$) and for DAs ($p<.001$), with no significant differences between HAs and DAs. Planned pairwise comparisons of non-significant interactions (group and array, drug and array, and group, drug and array) revealed the same pattern in performance levels between array types for both placebo and nicotine conditions.

RT analysis revealed no significant drug or group main effects. A main effect of array type on RTs ($F$ [2, 44] = 99.95, $p<.001$) was observed, with follow-up pairwise comparisons showing that RTs were longest ($p<.001$) for TAs, intermediate for DAs and shortest for the HAs. Planned pairwise comparison of 2-way and 3-way non-significant interactions revealed the same pattern in RT between array types for both placebo and nicotine conditions.

### 3.2. Exploring the presence of N2pc component

Grand averaged ERP waveforms (collapsed across drug conditions) obtained for arrays containing a target are shown in Fig. 2 for the parietal (P3/P4), occipital (O1/O2) and temporo-parietal (P7/P8) electrode sites. Consistent with the waveforms, ANOVAs conducted for TAs reflected the presence of the N2pc component by significant main effects of laterality ($F$ [1, 22] = 35.58, $p<.001$) and region ($F$ [2, 44] = 7.63, $p<.001$), with the contralateral hemisphere ($M$ = −.31 μV, $SE$ ± .63) showing a greater ($p<.001$) effect than ipsilateral ($M$ = 1.20 μV, $SE$ ± .54) and with occipital electrodes showing the largest amplitude ($M$ = −.17 μV, $SE$ ± .81) compared to temporo-parietal ($M$ = .06 μV, $SE$ ± .57) and parietal electrodes ($M$ = 1.42 μV, $SE$ ± .44). Additionally, a significant interaction between target field and group ($F$ [1, 22] = 4.61, $p<.05$) was observed, though this effect disappeared with a follow-up pairwise comparison. Lastly, a trend ($F$ [1, 22] = 3.89, $p = .061$) was observed for the drug × group interaction. Follow-up pairwise comparisons revealed a greater ($p<.05$) N2pc amplitude during nicotine (M = −.035 μV, $SE$ ± .88) compared to placebo ($M$ = .78 μV, $SE$ ± .81) administration in HPR individuals. LPR individuals did not exhibit a difference in N2pc amplitude between nicotine and placebo administration.

Planned comparisons were carried out to examine the specific study hypothesis regarding N2pc amplitudes elicited by target arrays. Within the group × drug × laterality × electrode interaction, planned comparisons for HPR individuals revealed a greater ($p<.05$) N2pc amplitude in the nicotine condition ($M$ = −1.58 μV, $SE$ ± 1.02) compared to placebo condition ($M$ = −.25 μV, $SE$ ± .97) at temporo-parietal contralateral electrode sites. Fig. 3 illustrates grand averaged ERP waveforms elicited in response to orientation targets for HPR and LPR individuals during nicotine and placebo conditions.

### 3.3. N2pc difference amplitude

A significant main effect was found for region, ($F$ [2, 44] = 16.27), $p<0.01$, with temporo-parietal regions ($M$ = −.92 μV, $SE$ ± .10) showing greater amplitudes compared to occipital ($M$ = −.70 μV, $SE$ ± .93) and parietal ($M$ = −.61 μV, $SE$ ± .67). Planned comparisons were carried out to examine the specific study hypothesis regarding N2pc difference amplitudes elicited by TAs. Within a group × drug × region interaction, planned comparisons for HPR individuals revealed a trend in the parietal ($p = .063$) and temporo-parietal ($p = .073$) electrode sites for nicotine to be associated with a greater N2pc difference amplitude compared to placebo. In contrast, LPR individuals showed an opposite drug effect ($p<.05$) in the temporo-parietal electrode sites, such that placebo ($M$ = −2.63 μV, $SE$ ± .45) resulted in a greater N2pc difference amplitude compared to nicotine ($M$ = −2.09 μV, $SE$ ± .51). Fig. 4 shows grand averaged N2pc difference waveforms in response nicotine and placebo administration in HPR and LPR individuals.

### 3.4. Color non-target amplitude (DAs)

Analysis conducted for DAs revealed that the difference in mean amplitude between the waveforms obtained for arrays with ipsilateral versus contralateral color singleton was not significant in the N2 latency range. This finding confirms the general observation that irrelevant color DAs did not elicit an N2pc component. This result suggests that the irrelevant color singleton did not produce an automatic orienting of attention to their location.

### 3.5. HA, DA, TA comparison

In order to further explore this issue, we compared the ERP waveforms obtained for HAs with those obtained for TAs and DAs. A new ANOVA was performed in which the three array types were included. Trials with left and right visual field pop-outs were collapsed (amplitudes were averaged) in this analysis to permit the comparison with HAs. A significant ($p<.001$) effect of array type ($F$ [2, 44] = 25.59, $p<.001$) on N2 component was higher for arrays containing targets ($M$ = −.31 μV, $SE$ ± .64) than for the other two array types, with no significant difference in N2 amplitude between DAs ($M$ = 1.05 μV, $SE$ ± .49) and HAs ($M$ = .97 μV, $SE$ ± .49). These results indicated that TAs received additional processing compared to the other two array types, and that DAs and HAs were not differentially processed.

### 3.6. Self-reported measures

No significant effects of drug or group were observed on alertness and calmness dimensions. Contentedness showed a significant main

**Table 1**
Mean RTs, percent hits and standard error for homogenous arrays, color non-target arrays, and orientation target arrays during placebo and nicotine conditions.

| Drug | | Homogeneous | | Orientation target | | Color non-target | |
|---|---|---|---|---|---|---|---|
| Placebo | Performance | Mean | SE | Mean | SE | Mean | SE |
| | % hits | 98.68 | ±.77 | 92.21 | ±1.71 | 98.16 | ±.74 |
| | RT (ms) | 425.41 | ±13.68 | 509.09 | ±8.42 | 454.91 | ±10.24 |
| Nicotine | % hits | 98.41 | ±.78 | 90.07 | ±2.07 | 97.93 | ±.66 |
| | RT (ms) | 431.93 | ±9.29 | 507.42 | ±8.61 | 462.50 | ±10.31 |

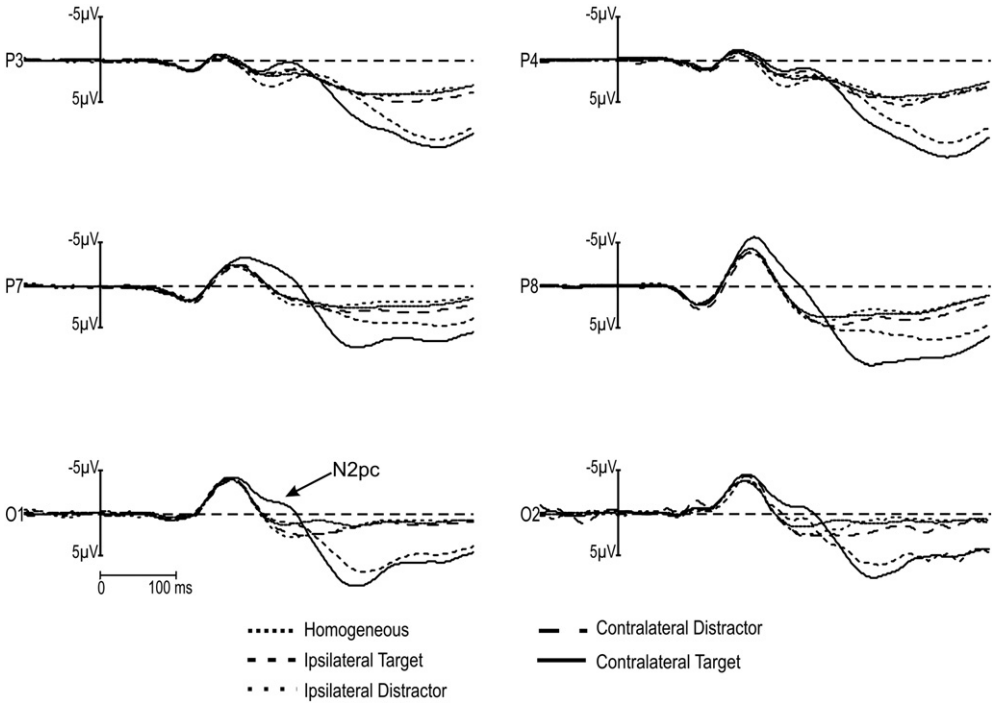


**Fig. 2.** Grand average ERPs elicited in response to arrays containing homogenous arrays, an orientation target (TA) and color distractor (DA) in the contralateral or ipsilateral visual field to electrode location. The grand averaged waveforms were collapsed across drug conditions. The ERPs obtained from the left and right posterior electrodes are displayed separately. The N2pc component is visible as a more negative response for the contralateral waveform relative to the ipsilateral waveform in the N2 latency range.

effect of group, $F\,(1, 22) = 7.82$, $p < .05$, with HRP individuals reporting greater contentedness ($M = 6.70$, $SE \pm .30$) compared to LRP individuals ($M = 5.52$, $SE \pm .30$). There was also a significant main effect of drug factor on adverse events ($F\,[1, 22] = 4.39$, $p < .05$), with nicotine condition ($M = 1.58$, $SE \pm .17$) resulting in greater symptom severity compared to placebo condition ($M = 1.17$, $SE \pm .10$). Post nicotine administration, 15 participants reported experiencing "No symptoms at all", 4 participants reported experiencing "Mild symptoms (i.e. slight jitters)" and the remaining 5 participants reported experiencing "Moderate symptoms (i.e. jittery, slight dull headache)". No group differences were observed on the adverse events ratings.

### 3.7. Vital signs measures

There was a main effect of drug on heart rate (HR), $F\,(1, 23) = 5.07$, $p < .05$, with nicotine ($M = 69.38$ bpm, $SE \pm 1.64$) showing a greater increase in HR compared to placebo ($M = 66.04$ bpm, $SE \pm 1.64$). A planned pairwise comparison revealed a significant difference between

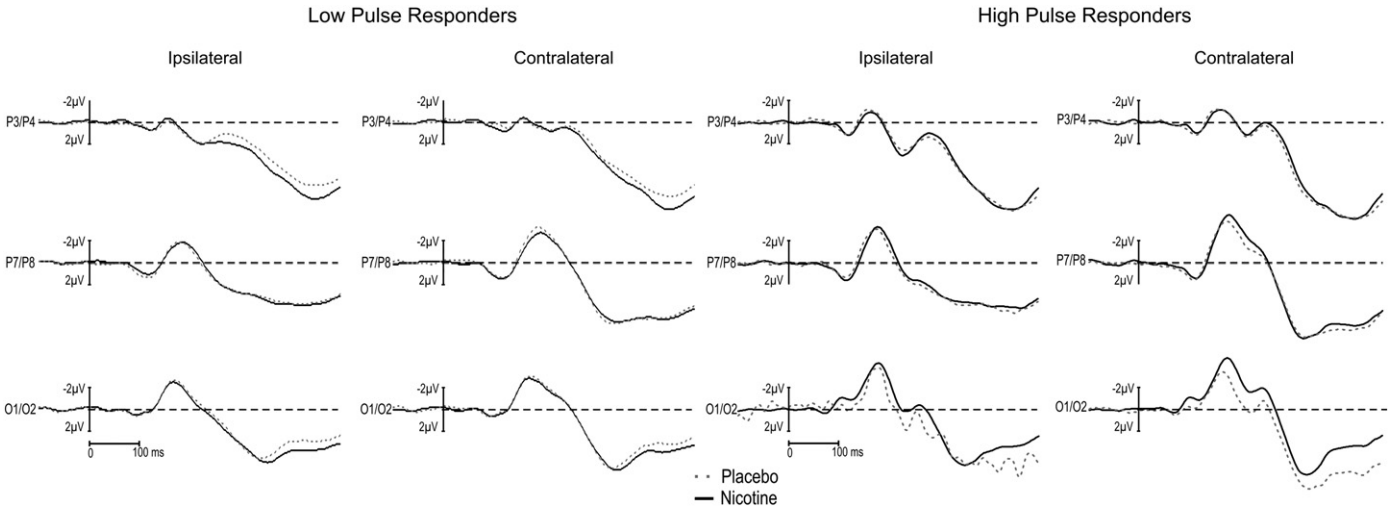


**Fig. 3.** Grand average ERP waveforms elicited in response to orientation targets in the ipsilateral and contralateral target visual field to electrode location. ERPs for high pulse rate and low pulse rate individuals, elicited during nicotine and placebo conditions are overlapped.

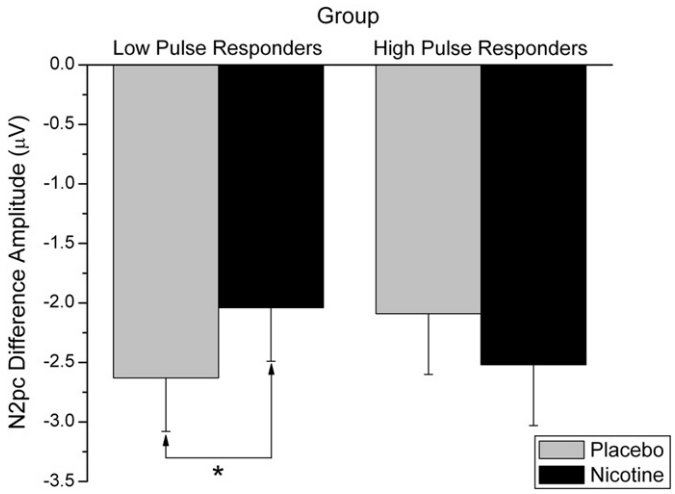


**Fig. 4.** Grand averaged N2pc difference amplitude elicited in response to nicotine and placebo administration in high pulse rate and low pulse rate individuals. Amplitudes obtained from the temporo-parietal region. *$p<.05$.

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, $SE\pm1.74$). There were no drug effects observed on DBP or SBP.

## 4. Discussion

### 4.1. Summary of study findings

This is the first investigation to examine the effects of nicotine in non-smokers on behavioral and neural processing of location targets in a visual search task. This study aimed to evaluate the acute effects of nAChR agonist treatment on selective visual spatial processing by assessing ERPs and behavioral performance in non-smoker groups that differed in their somatic responsiveness to nicotine. The N2pc component was assessed during a visual search task to elucidate neural mechanisms underlying the putative attentional enhancing properties of nicotine.

The visual search paradigm was effective in eliciting the characteristic morphology and scalp topography that typically describes N2pc with the long latency negativity appearing in posterior contralateral hemisphere within the designated latency window after the stimulus onset. As has been previously reported, the N2pc component was only present for target arrays and was found to be maximal over the occipital sites, contralateral to the stimulus (Luck and Hillyard, 1994a, 1994b; Lorenzo-López et al., 2008).

Contrary to our hypothesis and the visual search literature (Rycroft et al., 2005), nicotine did not exert effect on response speed or response accuracy measures of behavioral performance. Many studies have reported improved reaction times and increased target detection accuracy with both acute smoking and nicotine administration during varied visual attention tasks including paradigms involving visual search (Baldinger et al., 1995; Foulds et al., 1996; Levin et al., 1998; Pritchard et al., 1992; Rycroft et al., 2005; Trimmel and Wittberger, 2004; Warburton and Mancuse, 1998). Though these studies on behavioral effects of nicotine have tended to employ both smoking and abstaining smokers, similar results have also been observed with non-smokers (Levin et al., 1998). Studies using an abstinent smoking population find more reliable behavioral results; however, this may simply reflect a return of withdrawal-induced impaired performance to normal performance (Heishman et al., 1994).

### 4.2. Nicotine and behavioral performance

The lack of effects of nicotine on behavioral performance corresponds with a number of previous studies on the acute effects of nicotine in subjects with an intact nAChR system and in non-smoking humans (Newhouse et al., 2004). These performance data support the suggestion that nicotinic receptor mechanisms underlying behavioral responses may be maximally activated in non-smokers performing this task, and indicate that the effects of acute nAChR agonist treatment would not result in any additional performance benefit for this group. Nicotine's ability to impact performance varies based upon dose and route of administration and task demands, therefore in the future a more complex task may result in more effective manipulation of reaction time and/or accuracy, as the visual search paradigm is a relatively easy task, with most participants achieving at least 75% accuracy on their first practice. A more difficult task, for example with an array containing both color non-target and orientation target, would exhaust more attentional demands (Duncan and Humphreys, 1998) and set the stage for correction by nicotine.

Additionally, the lack of nicotine effects on behavioral performance corresponds with a number of fMRI studies on the acute effects of nicotine on visuo-spatial attention, visual alerting and target detection tasks (Giessing et al., 2007; Thiel and Fink, 2007) in non-smoking humans. Nicotine can exert differential effects on the behavioral, physiological and neural levels and for a given task and a given dose of nicotine, effects may be better reflected in neural than behavioral data as evidenced with other drugs (Bullmore et al., 2003; Ghatan et al., 1998; Hershey et al., 2004). Changes at each level can provide information in its own right and significant nicotine-induced changes in brain activation without corresponding alterations in behavior can inform cognitive theory (Wilkinson and Halligan, 2004).

### 4.3. Acute nicotine effect on N2pc waveform

The visual search paradigm elicited a consistent N2pc component when subjects were presented with orientation targets. As in previous studies, this effect was manifested as a negative polarity in the posterior electrode sites contralateral to the attended visual hemifield in the typical N2 time range, with maximum amplitude located over the occipital lobe (Luck and Hillyard, 1994b; Woodman and Luck, 2003; Lorenzo-López et al., 2008). According to the literature, this component indicates a shift of visual spatial attention to predefined targets in the search array (Luck and Hillyard, 1994a, 1994b). A significant increase in N2pc amplitude, contralateral to the target field, was observed in HPR individuals during nicotine administration compared placebo in the temporo-parietal electrodes, thus supporting the hypothesis, at least at the neural level, that selection in visual search was enhanced by nicotine.

Information processing models of the human visual cortex have suggested that the N2pc index of visual spatial attention elicited in the selection of relevant target location emerges through a biased competition between target and distractor positions, with target location enhancement and distractor location suppression (Luck, 1994; Luck and Hillyard, 1994a; Luck et al., 1997a, 1997b). Visual spatial selection by location specific top-down mechanisms is assumed to be mediated through the dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex, brain regions, which form part of a cognitive control network that also includes regions in the medial frontal cortex such as the anterior cingulate cortex of pre-supplementary motor area (Cole and Schneider, 2007).

Although nAChRs are expressed and distributed widely throughout the cerebral cortex (Wevers, 2011), the finding that nicotine increased neural processing in the parietal region and not the behavioral (i.e., the planning and execution of a motor response) processing underlying target selection during visual search may indicate

a preferential activation of the posterior attentional system via nAChR stimulation. This observation parallels repeated functional magnetic resonance imaging (fMRI) findings of nicotine-altered parietal activity in cued visual spatial attention tasks with minimal or no improvement in behavioral performance (Giessing et al., 2006; Thiel et al., 2005; Vossel et al., 2008). The posteriorally enhanced N2pc seen with acute nicotine also parallels nicotinic binding and infrahuman performance reports, which have shown that although both nAChR agonists (Obinu et al., 2002) and tasks with explicit attentional demands (Arnold et al., 2002; Himmelheber et al., 2001) can release acetylcholine in the frontoparietal cortical regions, nicotine binding sites in the brain of nicotine-naive rats are highest in the parietal cortex, a region that contains the greatest density of high affinity (most likely the alpha4 nicotinic receptor subunit) nAChRs (Benwell and Balfour, 1985), which have been found to be selectively activated (vs. muscarinic receptors) in the parietal (and thalamic) regions during the central processing of visual tasks (Mentis et al., 2001).

### 4.4. Acute nicotine effects on N2pc difference waveform

The N2pc difference waveforms were calculated to isolate the N2pc from other overlapping components by subtracting the ERPs for arrays containing an ipsilateral target from those containing a contralateral target. The results obtained for the N2pc difference waveforms were consistent with those from the N2pc target waveforms and previous work (Lorenzo-López et al., 2008), with the striking exception that LPR individuals exhibited a reduced N2pc with nicotine compared to placebo. Although findings of cognitive decrements with acute nicotine have been reported (Newhouse et al., 2004), they tend to be rare, not associated with particular psychobiological traits, and are typically explained as being the result of a cortical hyperarousal state induced by nicotine. The high diversity of neuronal nAChR subunits can potentially lead to an enormous variety of nAChR subtypes with different sensitivity to nicotine (Rose et al., 2010). Acute administration of nicotine or nicotinic agonists initially activates nAChRs, which subsequently desensitize and then become inactive with prolonged exposure. nAChRs are then re-sensitized over a period of seconds to minutes, depending on the receptor subtype (Dani and De Biasi, 2001).

Compared to smoke-inhaled nicotine, which results in the fastest kinetics of nicotine accumulation in arterial blood (Rose et al., 2010), nicotine concentration dynamics for gum-administered nicotine is relatively slow and prolonged and as a result, is thought to favor nAChR desensitization/inactivation (Hukkanen et al., 2005). Although this is highly speculative without supportive pharmacokinetic data, if one assumes that brain nicotine bioavailability is relatively low in LPR participants, reduction in this group of the neural processing of the spatial location of visual targets that is indexed by nicotine-attenuated N2pc may well be related to nAChR desensitization as nAChRs in subthreshold concentrations of nicotinic agonists can cause the receptor to desensitize without its significant activation (Dani and Bertrand, 2007). Accordingly, the measured in vitro $EC_{50}$ values for activation (for nicotine, 0.5–100 μM) are in the range of at least one-order-of magnitude greater than the $EC_{50}$ values for desensitization (Kuryatov et al., 2008; Olale et al., 1997; Rose et al., 2010).

### 4.5. Concluding thoughts and limitations

Improvements in the localization of targets in visual space observed at the neural level, and reflected by the enhanced N2pc component during nicotine administration, may be attributed to nicotine's ability to engage nicotinic-modulated posterior brain systems mediating selective attention. We suggest that, in line with the 'stimulus filter' hypothesis (Kassel, 1997), nicotine narrows attention to the orientation target stimuli via two parallel processes: acting as a stimulus barrier, screening out irrelevant stimuli from awareness (distractor suppression) and in turn enhancing the processing of target locations, the effects of which result in larger N2pc amplitudes. The sensitivity of nAChR-modulated visual spatial attention to nicotine and other nicotinic agonists may vary as a function of dose as well as the functional status and subtype of the nicotinic receptor. As nicotine was administered to non-smokers, the study outcomes were 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. Although not a focus of this paper, individual differences in nicotine-modulated visual search have implications for nicotine dependence as attentional enhancement is believed to be a prime motivator of tobacco use in vulnerable populations (e.g. schizophrenia, attention deficit disorder) with marked deficits in this functional domain (Evans and Drobes, 2009).

Although we forward an argument suggesting that our symptomatic sub-groups stratified on the basis of nicotine induced heart-rate responsivity may indirectly index nicotine's central bioavailability, blood nicotine levels provide an objective marker of nicotine absorption. One must be mindful that peripheral venous blood levels of a drug do not necessarily reflect brain or arterial levels. Only one dose of nicotine was administered and future work needs to examine multiple doses (based on body weight) to derive dose–response effects of nicotine on visual spatial attention. Nicotine administered by gum can result in marked individual differences in absorption and blood nicotine levels and the relatively slow exposure to nicotine can exert unique nAChR actions unlike vehicles (e.g. cigarettes, nicotine inhaler, injections) associated with rapid nicotine delivery. The administration of ligands with different affinity to nAChR subtypes, particularly α4 and α7 would be of interest as each has been implicated extensively in attention but their differential role in visual spatial attention is still unknown. The present visual spatial search task made no attempt to manipulate stimulus (e.g. location, saliency of distractors and target stimuli) and/or response features to determine what specific processes (target enhancement or distractor suppression) are most sensitive to nicotine. Finally, analysis of scalp derived potentials by themselves does not specifically yield accurate information on the cortical origin of associated processes and/or drug actions. Additional studies employing source analysis strategies would help to localize N2pc cortical sources modulated by nicotinic systems.

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