Original Paper

Nicotine enhances an auditory Event-Related Potential component which is inversely related to habituation

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Theresa Veltri[1], Naira Taroyan[2] and Paul G Overton[1]

Abstract

Nicotine is a psychoactive substance that is commonly consumed in the context of music. However, the reason why music and nicotine are co-consumed is uncertain. One possibility is that nicotine affects cognitive processes relevant to aspects of music appreciation in a beneficial way. Here we investigated this possibility using Event-Related Potentials. Participants underwent a simple decision-making task (to maintain attentional focus), responses to which were signalled by auditory stimuli. Unlike previous research looking at the effects of nicotine on auditory processing, we used complex tones that varied in pitch, a fundamental element of music. In addition, unlike most other studies, we tested non-smoking subjects to avoid withdrawal-related complications. We found that nicotine (4.0 mg, administered as gum) increased P2 amplitude in the frontal region. Since a decrease in P2 amplitude and latency is related to habituation processes, and an enhanced ability to disengage from irrelevant stimuli, our findings suggest that nicotine may cause a reduction in habituation, resulting in non-smokers being less able to adapt to repeated stimuli. A corollary of that decrease in adaptation may be that nicotine extends the temporal window during which a listener is able and willing to engage with a piece of music.

Keywords

Music, pitch, nicotine gum, ERPs, P2 amplitude

Introduction

Nicotine is a psychoactive substance that is commonly consumed in the context of music. Cigarettes are prevalent among young adults (Conrad et al., 1992) and college students (Wechsler et al., 1998), a demographic that is known to be most engaged with music (Hargreaves and North, 1997) and to attend music festivals (Packer and Ballantyne, 2010; Woodward et al., 2014), where nicotine products are consumed (Mackul'ak et al., 2015). However, the reason why music and nicotine are co-consumed is uncertain. One possibility is that nicotine affects cognitive processes relevant to aspects of music appreciation in a beneficial way. Previous research has established that cholinergic systems are important for cognitive functioning and nicotine is a potent cholinergic stimulant that affects many central nervous system pathways, including the auditory pathway (Crawford et al., 2002). Nicotine has been reported to improve attention, learning, reaction time, problem solving, and stimulus evaluation and discrimination (Heishman et al., 1994; Le Houezec and Benowitz, 1991; Wesnes and Warburton, 1983).

Many of nicotine's performance-enhancing properties can be explained through its ability to shift brain-state arousal (Heishman et al., 2010; Wesnes and Warburton, 1983). That is, many of the cognitive improvements seen with nicotine are thought to be indirectly mediated by its mood-elevating and physiological arousal-inducing properties (Newhouse et al., 2004; Waters and Sutton, 2000), and indeed smokers have reported that arousal control is one motive for nicotine use (Gilbert, 1979). Several neuroscientific studies investigating nicotine's effects on auditory perception have confirmed nicotine's ability to enhance arousal and attention using functional magnetic resonance imagining (fMRI) (Smucny et al., 2015; Thiel and Fink, 2007) and magnetencephalography (Otsuru et al., 2012). Electrophysiological techniques, for example Event-Related Potentials (ERPs), have also supported nicotine's role as an enhancer of arousal and attention (Harkrider and Champlin, 2001).

In relation to auditory information processing, ERP components P1, N1, P2 and N2 are particularly implicated in arousal and attention. P1 occurs approximately 50 ms after the onset of a stimulus (Key et al., 2005) and is strongly affected by stimulus factors, such as intensity (Kaskey et al., 1980), as well as arousal (Harkrider and Champlin, 2001). Component N1 occurs approximately 100 ms after stimulus onset and is also affected by arousal (Harkrider and Champlin, 2001). In addition, it is enhanced by increased selective attention to basic stimulus characteristics (Hillyard et al., 1973).

P2 occurs approximately 180–250 ms after stimulus onset (Friedman and Meares, 1980). This component shares many characteristics with N1 and as such they are often examined together as the N1–P2 complex. For example, P2 is also implicated in arousal and attention (Harkrider and Champlin, 2001)

[1]Department of Psychology, University of Sheffield, Sheffield, UK
[2]Department of Psychology, Sociology and Politics, Sheffield Hallam University, Sheffield, UK

Corresponding author:
Paul G Overton, Department of Psychology, University of Sheffield, Sheffield S10 2TN, UK.
Email: p.g.overton@sheffield.ac.uk

and is sensitive to physical characteristics of stimuli, including pitch (Novak et al., 1992). Furthermore, it is sensitive to habituation processes (Ritter et al., 1968; Rust, 1977) and decreases as an indication of more efficient stimulus filtering (Knott, 1989). Finally, N2 occurs between 180 ms and 325 ms following the onset of auditory stimuli (Patel and Azzam, 2005). It is modulated by arousal and attention (Harkrider and Champlin, 2001) and is also associated with response inhibition (Jodo and Kayama, 1992; Kaiser et al., 2006).

Nicotine has been shown in previous studies to affect all four of these components of the auditory ERP (P1, N1, P2 and N2). P1, the component implicated in arousal and known to be sensitive to stimulus factors (Kaskey et al., 1980), has been shown to increase in amplitude in studies examining nicotine's effect on abstinent smokers using auditory stimuli (Knott, 1985b). However, others (e.g. Friedman and Meares, 1980) have failed to find a similar effect, and hence nicotine's effects on auditory-related arousal as measured by this component are unclear. Indeed, the cognitive function most consistently affected by nicotine is attention (Newhouse et al., 2004; Stolerman et al., 1995). One aspect of attention that is particularly influenced by nicotine is selective attention. N1, the ERP component strongly associated with attention, consistently increases in amplitude during auditory tasks of selective attention (Hillyard et al., 1973). In general, this effect is further enhanced by nicotine (Knott, 1985b, 1986), reflecting the drug's ability to improve attentional processes (Hillyard and Picton, 1979). P2, the component implicated in habituation processes (Ritter et al., 1968; Rust, 1977), consistently decreases as a result of nicotine in auditory tasks of selective attention (Friedman et al., 1974a; Knott and Harr, 1995). This may reflect a more efficient filtering process and an enhanced ability to disengage from irrelevant stimuli (Knott, 1985a, 1989).

The N2 component occurs in response to attended and unattended deviants and can reflect disparity between a deviant stimulus and a sensory-memory representation of the target stimulus. Early research with this component (Picton and Hillyard, 1974; Picton et al., 1974) suggests the amplitude of the auditory N2 to be inversely related to behavioural arousal and therefore to be significantly smaller during high activation states (Knott, 1989). Initial reports examining the influence of nicotine on ERPs using auditory stimuli reported a reduction of the P2–N2 wave. However, other studies have found no effect of nicotine on the amplitude of the N2 component and P2–N2 complex (Knott, 1985b; Knott et al., 1995), again suggesting (as with P1) some uncertainty concerning nicotine's action on this component and hence on the underlying cognitive processes.

In addition to the considerable uncertainty over nicotine's effects on certain ERP components (P1, N2), previous studies examining the effects of nicotine on auditory information processing have three significant problems, particularly in relation to music perception. First, many studies have used an abstinent smoker population. Hence, where relevant, it is unclear whether nicotine's effects on cognitive processes are a result of the reversal of withdrawal or a true interaction with some aspect of auditory perception and cognition. Secondly, some studies have used pulses and clicks as opposed to tones (e.g. Friedman et al., 1974b; Harkrider and Champlin, 2001; Knott et al., 2009a). Pulses and clicks lack the physical dimensions of music (e.g. loudness, pitch). Therefore, sound stimuli that incorporate a musical dimension may facilitate auditory perception better than pulses and clicks, and may therefore be more sensitive to the effects of nicotine. Finally, those studies that have used tones have only used pure tones (e.g. Domino and Kishimoto, 2002; Friedman and Meares, 1980; Friedman et al., 1974a; Jodo and Kayama, 1992; Knott, 1985a), which are rare in music, and most have used only manipulated intensity (loudness) (e.g. Knott, 1985b). Another dimension of music, which has yet to be examined, is pitch, a fundamental element of music (Spencer and Temko, 1988). The basic perceptual mechanisms involved in pitch processing and how pitch is analysed by the auditory system are well established (McDermott and Oxenham, 2008). For example, we know that variations in pitch (e.g. high pitch, low pitch) are easy to perceive and discriminate (McAdams, 1989). Therefore, the current study will use pitch in combination with complex tones in order to investigate how nicotine affects auditory perception and cognition.

The aim of the present study is to test whether nicotine affects auditory information processing in non-smokers and, if so, to identify which cognitive mechanisms underlie the effect, in order to better understand the co-consumption of music and nicotine. Several different paradigms have been used to test the effects of nicotine on auditory perception in non-smokers, including passive listening (Harkrider and Champlin, 2001), discrimination (Knott et al., 2009a) and dichotic listening (Knott et al., 2009b). Again, this variation may account for the different ERP results found across these studies. With this in mind, a simple and repetitive task was employed for the current study where participants were asked to make a decision based on the combination of auditory and visual stimuli presented. A decision-making paradigm requires attention (and hence keeps participants focused on listening to the auditory stimuli) while stimulus repetition is conducive to habituation. This allows us to assay these cognitive mechanisms during nicotine and placebo conditions.

Method

Participants

Initially, 36 (18 male) participants were recruited with a mean age of 21.33 years, (SD = 3.25; range 18–29). Four participants were subsequently excluded due to lack of ERP responses or electrical noise during data acquisition, hence the data presented below are the result of the remaining 32 participants (16 per group). Participants either received credits as undergraduate psychology students or were paid £10 for one hour and 15 minutes of their time. The research protocol met the ethical requirements of the University of Sheffield's Ethics Committee.

All participants were free of neurological and psychiatric illnesses based on self-reports and none were pregnant or breastfeeding, all contraindications against the use of nicotine gum (Baldeweg et al., 2006). No participants reported substance dependence and none were taking medication (with the exception of an oral contraceptive). All participants were native English speakers with minimal exposure to secondary languages. Language background was controlled for because it is known to strongly influence auditory processing (Salmelin et al., 1999; Vihla et al., 2002) and exposure to a tonal language is particularly known to increase pitch perception (Krishnan et al., 2005). Therefore, competency of secondary languages was assessed

through self-reports of listening, speaking, reading and writing. Those who considered themselves to be above 'fair' in terms of their listening, speaking, reading and writing of a second language were excluded from participation. Volunteers were also excluded if they reported any experience with a tonal language, such as Mandarin or Vietnamese.

In order to control for hemispheric specialization (Alexander and Polich, 1997) and to conform to previous research methods (Wioland et al., 1999), all participants were right-handed, as defined by a score of 80–100% on the Edinburgh Laterality Test (Oldfield, 1971). Furthermore, because musical training has been repeatedly shown to improve pitch processing (Besson et al., 2007), and musicians in particular are thought to have superior pre-attentive auditory processing (Koelsch et al., 1999), musicians were excluded from the study. All participants were non-musicians defined as having no regular experience with playing a musical instrument and no musical training beyond mandatory music lessons in primary and secondary school.

Last, in order to avoid the potential confounding effects of pre-exposure to nicotine, all participants were non-smokers. Participants were required to have been entirely nicotine free for at least one year. This included habitual as well as occasional use, such as social smoking and shisha.

Pure tone audiometry

A pure tone audiometry (PTA) hearing test was used to check for any signs of hearing loss and to confirm that participants could detect stimuli. The PTA hearing test was used based on previous research by Light and colleagues (2010). The test was performed at ~80 dB SPL and consisted of tones at 125 Hz, 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, 8000 Hz and 10,000 Hz. The test was performed twice, once in each ear. Participants would have been excluded if they were unable to detect any tones in either ear or if they had gross abnormalities or asymmetries in their hearing between ears. No participants were excluded for these reasons.

Auditory stimuli

Sound stimuli were constructed based on previous research examining auditory perception using ERPs and mismatch negativity (Baldeweg et al., 2006; Tervaniemi et al., 2005). Sound stimuli consisted of two spectrally complex tones, one high and one low. The high pitch tone consisted of its fundamental frequency, 523.25 Hz (C5 on the Western scale) and its following four overtones of the harmonic series: 1046.50 Hz, 1567.98 Hz, 2093.00 Hz and 2637.02 Hz (C6, G6, C7 and E7 respectively on the Western scale). The low pitch tone consisted of its fundamental frequency, 130.81Hz (C3) and its following four overtones of the harmonic series: 261.63 Hz, 392.00 Hz, 523.25 Hz and 659.25 Hz (C4, G4, C5 and E5 respectively). The tones contained harmonics as previous behavioural and neural research have shown complex tones to better facilitate pitch processing compared with fundamental frequencies only (Tervaniemi et al., 2000a, 2000b). The stimuli were synthesized using Ableton Live 9.1 Suite, a software music sequencer, on a MacBook Pro, 2014. All sounds had a presentation time of 300 ms with a 5 ms rise and fall time, similar to previous research methods (Koelsch et al., 1999). Sounds were presented binaurally via insert earbuds at ~80 dB SPL.

Procedure

Prior to the experiment, participants undertook a health screening questionnaire to determine their eligibility to participate. Upon approval, participants were asked to refrain from all products containing nicotine, caffeine and alcohol for 24 h before the experiment. At the start of the electroencephalography (EEG) study participants were randomly assigned to either the nicotine or placebo condition and were given the appropriate piece of gum to chew, either nicotine (4 mg nicotine polacrilex gum – Boots NicAssist ice mint flavoured gum; $N = 16$) or placebo (Wrigley's Extra peppermint flavoured chewing gum, having similar size, shape and colour to the nicotine gum; $N = 16$). Participants were instructed to chew the gum on a chewing–resting cycle of 30 s. That is, they chewed the gum for 10 s, then rested the gum on the inside of the cheek for 20 s. This cycle – the chewing method used previously in nicotine research (e.g. Ernst et al., 2001) – was repeated for 25 min. Resting the gum inside the cheek allows the nicotine to gradually be absorbed by the buccal mucosa and released into the blood stream. Four milligram nicotine gum yields levels comparable to smoking a commercial cigarette and it stays in the blood stream for over 120 min (Benowitz et al., 1988).

To help participants stay on task during the chewing–resting cycle, a video was played that mirrored the action of chewing or resting. When the subject was to chew gum, a high tone bell rang and an image of a mouth chewing gum appeared. When the subject was to rest, a low alarm tone sounded and an image of a stop sign with a halt hand in the centre appeared. While participants were engaged in the chewing–resting cycle, they were fitted with the EEG net and the sensors were checked for impedance levels. At the end of the 25 min, a final image of a chewed piece of gum appeared and a message over the top read 'Please spit out gum'. At this time participants discarded the gum and prepared to begin the auditory perception task. They did this by centring themselves 50 cm in front of the computer screen and by having earbuds fitted into their ears and checked for sound.

For safety reasons, adverse effects were also monitored through self-report. Upon completion of the chewing–resting cycle, participants were administered the Subjective Treatment Emergent Symptom Scale, which assesses the physical reactions to nicotine and the severity of these reactions (Guy, 1976). Participants with scores of 50% or more on any of the four subscales were discontinued from the study. Two participants were discontinued for this reason and were replaced.

Before beginning the task, participants were introduced to general aspects of the experimental procedure. Participants were told that a fixation cross would appear on the computer screen, followed by a sound. After this an image of two arrows facing in opposite directions (one up, one down – the up and down arrows could be on the left or on the right) would appear and that based on the arrangement of these arrows they would be asked to indicate a response on a keypad using their index fingers. They were also told that after their response the procedure would repeat.

Participants were then introduced to the auditory and visual stimuli used in the experiment, which were presented using E-prime 2.0 software (Psychology Software Tools, Pittsburgh, PA, USA). Participants first listened to the high pitch and low pitch tones separately. Next, participants were shown the arrow images and further details of the procedure were explained, namely that they would hear a tone (either high pitch or low

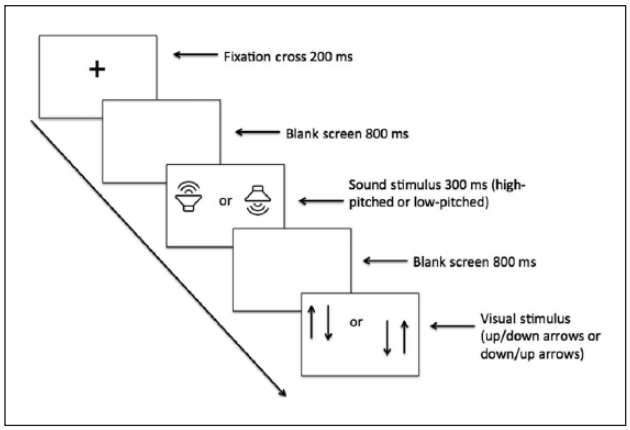


Figure 1. The experimental procedure. Subjects fixated a cross which was followed 200 ms later by a blank screen for 800 ms. After that, a tone was presented for 300 ms – either high pitch or low pitch – followed by another 800 ms of blank screen before the visual stimulus, consisting of an up arrow and a down arrow. If they heard a high pitch sound, they were to focus on the position of the up arrow. If the up arrow was positioned on the left-side of the image, then they were to press '1' on the keypad; if the up arrow was positioned on the right-side of the image, then they were to press '4'. Alternatively, if they heard a low pitch sound, they were to focus on the position of the down arrow. If the down arrow was positioned on the left-side of the image, then they were to press '1'; if the down arrow was positioned on the right side of the image, then they were to press '4'.

pitch) followed by one of the arrow images. If they heard a high pitch sound, they were to focus on the position of the up arrow. If the up arrow was positioned on the left-side of the image, then they were to press '1' on the keypad; if the up arrow was positioned on the right-side of the image, then they were to press '4'. Alternatively, if they heard a low pitch sound, they were to focus on the position of the down arrow. If the down arrow was positioned on the left-side of the image, then they were to press '1'; if the down arrow was positioned on the right side of the image, then they were to press '4'. Figure 1 illustrates this procedure and displays the duration (in ms) of each event.

In order to record the highest quality of EEG data, participants were requested to refrain from blinking as best they could during presentation of the fixation cross and sound and instead to try to blink during the arrow images or while responding with the keypad. After these verbal instructions, the lights were turned off and participants were left alone in the room. In order to reiterate the experimental instructions, the procedure for the experiment was written out on the computer and participants were given practice trials consisting of two blocks of eight trials each. After practising, the experiment began, consisting of four blocks of 100 trials each. In between blocks, participants were allowed to rest for as long as they liked. Rest periods were employed in order to maximize concentration during the experiment. At the end of the experiment participants were detached from the EEG net and debriefed.

Data acquisition

Electrophysiological data were recorded continuously from the scalp using a 128-channel Geodesic Sensor Net (GSN) (Tucker, 1993) from Electrical Geodesics, Inc. (EGI, Eugene, OR, USA). The GSN is a lightweight knitted network of elastic threads that house electrodes in small plastic pedestals. Inside each pedestal is an Ag/AgCl synthetic sponge sensor that serves to detect and record the electrophysiological data. The sponges are soaked in a solution of potassium chloride in order to render them conductive (Casanova et al., 2012). The GSN has an even inter-electrode distance of 2.7 cm and a C_z reference at the vertex of the scalp (Sabbagh et al., 2004). The six most anterior electrodes of the GSN record the horizontal and vertical electroculogram, monitoring eye movements and blinks. The GSN connects to the EGI high-input impedance amplifier (200 MΩ, Net Amps, Electrical Geodesics, Inc., Eugene, OR, USA) with an in-line finite impulse response bandpass filter of 0.1–400 Hz. Individual electrodes were adjusted in order to keep impedance below 50 kΩ, as recommended by the manufacturer. Channel signals were amplified × 1000 and digitized with a 12-bit A/D converter at a sampling rate of 1000 Hz (1 ms samples). The EEG data, as well as event onset times, were collected and stored on a Macintosh G4 (10.2.8) using EGI Net Station 4.1.2 for further analysis. Data acquisition sessions lasted for approximately 30 min for a typical recording.

Data analysis

Subsequent processing and analyses were performed offline. Data were digitally filtered with a bandpass of 1–50 Hz. A high pass-filter of 1 Hz was used in order to exclude any slow direct current shifts, while a low pass-filter of 50 Hz was used in order to remove any mains interference. Segmentation of the continuous EEG data was performed using an epoch that began 100 ms prior to the onset of the sound stimulus and ended 400 ms after. Next, artefacts were removed from the epochs. This was first achieved automatically by employing Net Station's artefact detection routine. That is, individual channels within each epoch were marked as 'bad' if they contained either zero variance, a fast average amplitude exceeding 200 μV, or a differential average amplitude exceeding 200 μV. Furthermore, individual epochs were rejected if they contained eye movements, identified by a maximum to minimum differential of 70 μV, or blinks, identified by a maximum to minimum differential of 100 μV. All segments were then subjected to a visual inspection in order to identify and remove any remaining artefacts that did not exceed the threshold values. Individual segments were rejected if they contained more than 10 bad channels. For the remaining segments, individual bad channels were replaced with a spherical spline algorithm (Srinivasan et al., 1996), which interpolates data for bad channels using data of the surrounding channels. Ninety per cent of the segments were retained. The number of artefact-free epochs was comparable across groups (placebo, high pitch: M = 142.00, low pitch: M = 141.27; nicotine, high pitch: M = 151.19, low pitch: M = 151.81).

The remaining trials were then segregated by condition (high pitch; low pitch) and averaged for each participant. The ERPs obtained for both high pitch and low pitch stimuli were taken regardless of whether the correct keypad response was given by the participant, because the decision-making aspect of the experiment and the subsequent response was only used to keep participants focused on listening to the auditory stimuli and to conceal the true nature of the experiment.

Next, all ERPs were baseline-corrected. This was performed for each channel by taking the average of all the samples within the 100 ms of pre-stimulus data and subtracting it from all the remaining samples (stimulus onset to 400 ms post-stimulus). Finally, the individual participants' ERPs were re-referenced in order to correct for the polar average reference effect (PARE; Junghöfer et al., 1999). Voltage measurements from EEG are measurements of the difference in potential between the site being measured (a specific electrode) and the reference site (C_z), which is assumed to have a voltage of zero. However, the surface of the scalp is unevenly sampled because electrodes are concentrated on the top of the head. This causes the average reference to be biased towards the top of the head and results in differences in the average to be smaller at the vertex than at the periphery. This bias – the PARE – must be corrected. Using a spherical spline interpolation, the voltages of the surface of the scalp not covered by electrodes can be estimated. Using the results from this interpolation, a PARE-corrected average reference was calculated for the entire surface of the scalp. After re-referencing, group averages of ERPs were calculated separately for the nicotine and placebo groups for both the high pitch and low pitch conditions.

Statistical analysis

The ERP components of interest were P1, N1, P2 and N2. They were identified through visual inspection of group averages and individual data. Furthermore, they were found to be most distinct and of largest absolute amplitude in the frontal and central regions of the scalp. The time windows chosen for each component were based on previous literature (Key et al., 2005; Picton and Hillyard, 1974) as well as visual inspection of the data. These were: P1, 30–70 ms; N1, 80–120 ms; P2, 140–200 ms; N2, 240–300 ms.

The mean amplitude and latency of the P1, N1, P2 and N2 components from the frontal and central regions of the scalp were statistically analysed for the left, central and right areas. For the left and right areas of the frontal and central regions a group of channels (electrodes) were averaged together to derive the mean amplitude and latency of each group of channels. Averaging a group of neighbouring electrodes is a standard approach taken in ERP analyses (Baruth et al., 2010; Picton et al., 2000) and is done in order to improve the signal to noise ratio, thereby increasing the statistical power of the data (Oken and Chiappa, 1986). These channel groups and their relation to the 10–20 International System (Jasper, 1958) are presented in Figure 2. The channel groups for the left and right areas of the frontal region (those areas encircled in Figure 2) were based on those used in previous research (Baruth et al., 2010; Casanova et al., 2012; Maitre et al., 2012). These areas correspond to F_3 and F_4 of the 10–20 International System and are therefore given these names in the current study, and along with F_z formed the channels of interest for the frontal region. The channel groups for the left and right areas of the central region (those areas squared in Figure 2) were also based on previous literature (Maitre et al., 2012; Yokota et al., 2014). However, compared with previous literature, the current study's grand average waveforms showed the left and right areas of the central region to have maximal activation closer to the vertex. Therefore, the channel groups used for these areas have been moved inward

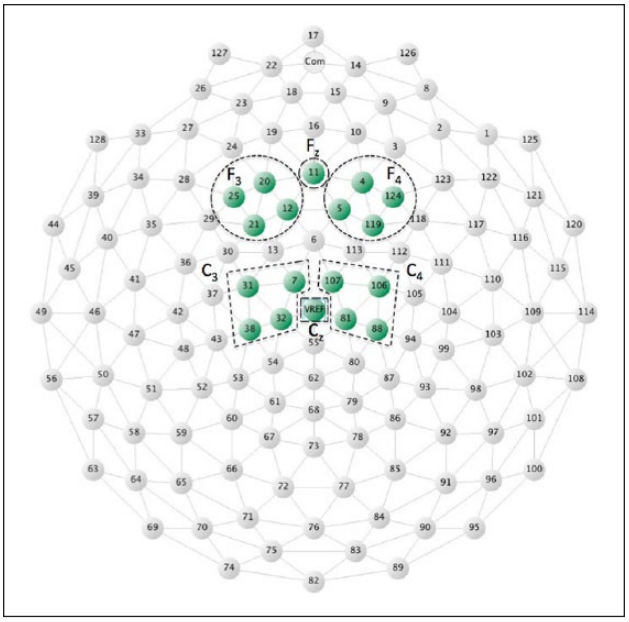


Figure 2. Channel/channel groups selected for analysis. A representation of the electrodes grouped together in the frontal region (upper circled channel groups) and central region (lower squared channel groups). These channel groups are further divided by hemisphere and midline. Their approximate locations corresponding to the 10–20 International System (Jasper, 1958) are labelled (e.g. F_3, F_z, F_4; C_3, C_z, C_4) next to each channel group.

compared with past research. For this reason, C_3 and C_4 of the 10–20 International System are not contained within the central region's left and right channel groups, respectively. However, because these groups approximately correspond to C_3 and C_4 they are given these names. C_z (also a channel of interest in the central region) in the current study corresponds to C_z of the 10–20 International System and therefore is given this name.

Peak amplitudes in individual subjects' ERPs were found within the time window and peak latency was calculated relative to the stimulus onset. Where channels were grouped, the peak amplitude and latency from all electrodes in a channel group were averaged. Figure 3 shows those waveforms used in the current analysis – the peripheral waveforms are representative of each channel group (and F_z and C_z) and show the characteristic ERP components P1, N1, P2 and N2. These data are shown again on a larger scale in Figure 4.

For each individual participant, the amplitude was calculated for each component (P1, N1, P2, N2) in each region of interest (frontal/central; left, centre, right – F_z and C_z constitute 'centre' here) and was then analysed by means of a repeated-measures analysis of variance (ANOVA). This same procedure was repeated for latency information. This led to 16 separate ANOVAs: 4 components × 2 ERP measurements × 2 scalp regions. For each ANOVA, there were two within-subjects factors: (1) sound (high pitch and low pitch) and (2) area (left, right, and central). There was also one between-subject factor, drug condition (placebo or nicotine). Where variables were found to violate the assumption of sphericity a Greenhouse–Geisser correction was used. Probabilities at the level of $p < 0.05$ were considered to be significant. For post-hoc analyses, Bonferroni correction was employed.

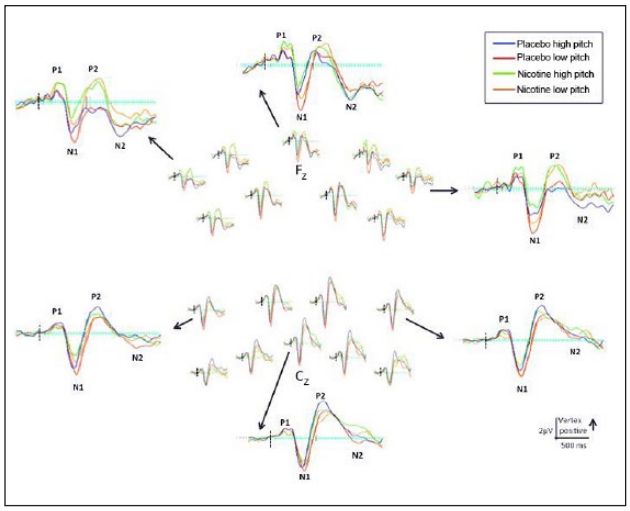


Figure 3. Analysis montage showing waveform averages for the channels/channel groups used in analysis. The inner part of the figure (smaller waveforms) shows the waveform averages for the different conditions at each of the relevant electrodes. Larger scale waveforms around the periphery show waveform averages for a representative from each channel group.

Results

ERP data

The grand average waveforms for the high pitch and low pitch conditions at the chosen recording sites are presented for the nicotine and control group in Figure 3. An expanded waveform can be viewed for the frontal areas, F_3, F_z and F_4 as well as for the central areas, C_3, C_z and C_4 in Figure 4. Furthermore, the mean amplitude and latency values for each component by condition and area are presented separately for the frontal (Figure 5) and central (Figure 6) regions.

P1. The amplitude and latency of the ERP components P1, N1, P2 and N2 was selected for statistical analysis as previously described. Repeated measures ANOVAs with three factors (pitch condition, area, drug group) were performed separately for the frontal and the central regions, and revealed some significant findings. For P1 amplitude in the frontal region, there was a main effect of area, $F(2,52) = 6.21$, $p = 0.01$, $\eta^2 = 0.19$, where P1 amplitude at F_z was significantly larger ($M = 0.95$, SEM = 0.12) than F_3 ($M = 0.73$, SEM = 0.10), $p = 0.01$. For P1 amplitude in the central region, there was also a main effect of area, $F(2,58) = 5.23$, $p = 0.008$, $\eta^2 = 0.15$, where P1 amplitude at C_z was significantly larger ($M = 0.76$, SEM = 0.10) than C_3 ($M = 0.62$, SEM = 0.08), $p = 0.02$.

For P1 latency in the frontal region, there was a main effect of area, $F(2,52) = 3.39$, $p = 0.041$, $\eta^2 = 0.12$. However, post-hoc tests revealed no significant differences between F_3 ($M = 46.85$, SEM = 2.00) and F_z ($M = 49.01$, SEM = 1.82), $p = 0.480$, between F_3 and F_4 ($M = 50.87$, SEM = 1.78), $p = 0.106$, or between F_z and F_4, $p = 0.482$. For the P1 latency in the central region no significant effects were found.

In summary, P1 amplitude was larger at the midline (F_z and C_z) compared with the left and right hemispheres. However, neither nicotine nor pitch affected P1 amplitude or latency. The main effect of area can be viewed in waveform and topographic form in Figures 4 and 7 respectively (the data are further summarized in Figures 5 and 6).

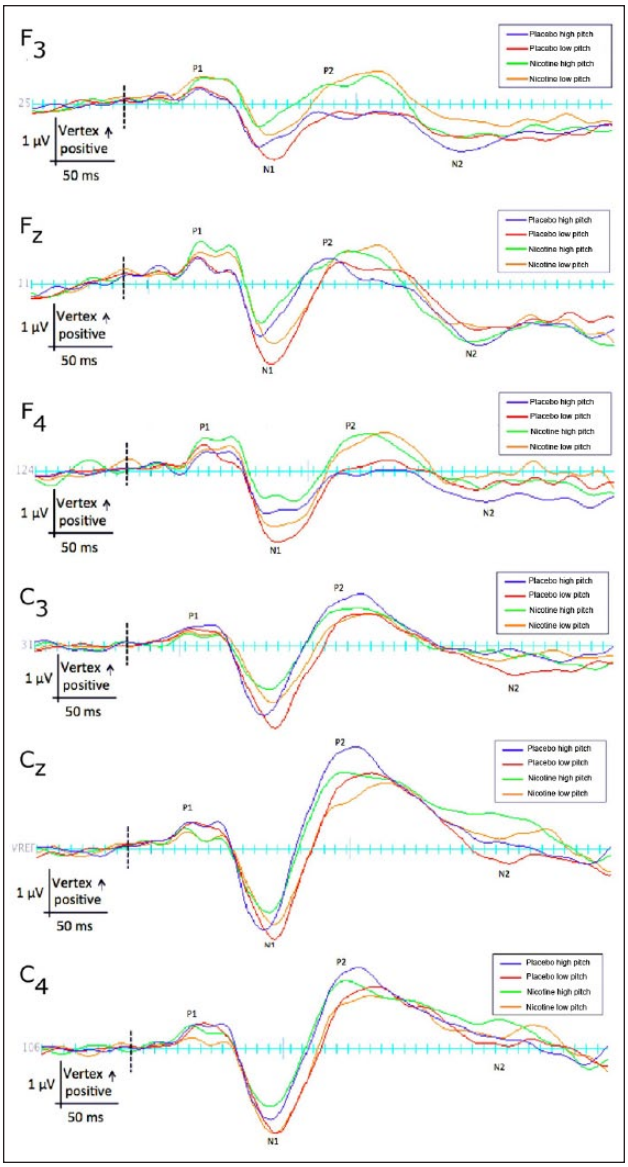


Figure 4. Waveform averages for the six channels/channel groups used in the analysis. In each case, the averages are shown separately for each condition (nicotine/placebo, high pitch/low pitch). The Event-Related Potential components of interest (P1, N1, P2, N2) are also shown for each channel/channel group.

N1. For N1 amplitude in the frontal region, there was a main effect of pitch, $F(1,28) = 6.20$, $p = 0.02$, $\eta^2 = 0.18$, where N1 for low pitch had a significantly larger amplitude ($M = -1.85$, SEM = 0.25) than high pitch ($M = -1.47$, SEM = 0.15). For N1 amplitude in the central region, there was a main effect of area, $F(2,58) = 4.34$, $p = 0.018$, $\eta^2 = 0.13$, where N1 amplitude at C_z was significantly larger ($M = -1.92$, SEM = 0.22) than C_3 ($M = -1.62$, SEM = 0.17), $p = 0.027$. There was also an interaction of area and

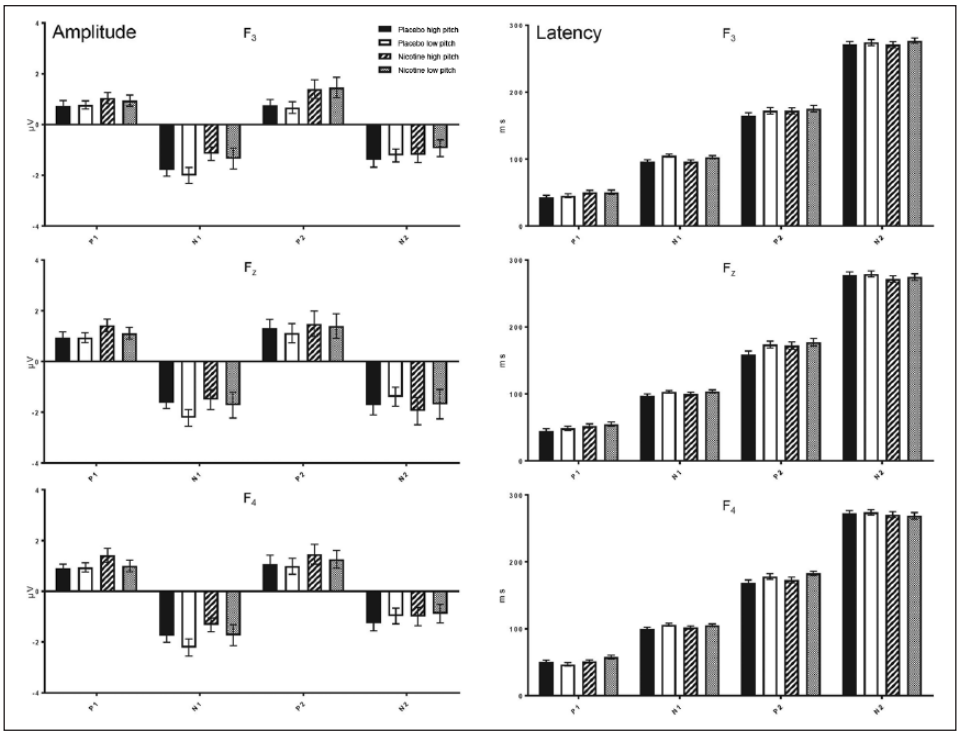


Figure 5. Amplitude (group mean values (mean ± SEM) in μV) and latency (in milliseconds; ms) of Event-Related Potential (ERP) peaks in the frontal region, for the nicotine and placebo groups across the two pitch conditions (high and low). Note: P1, N1, P2 and N2 are ERP components; F_3, F_z, F_4 are electrode groups.

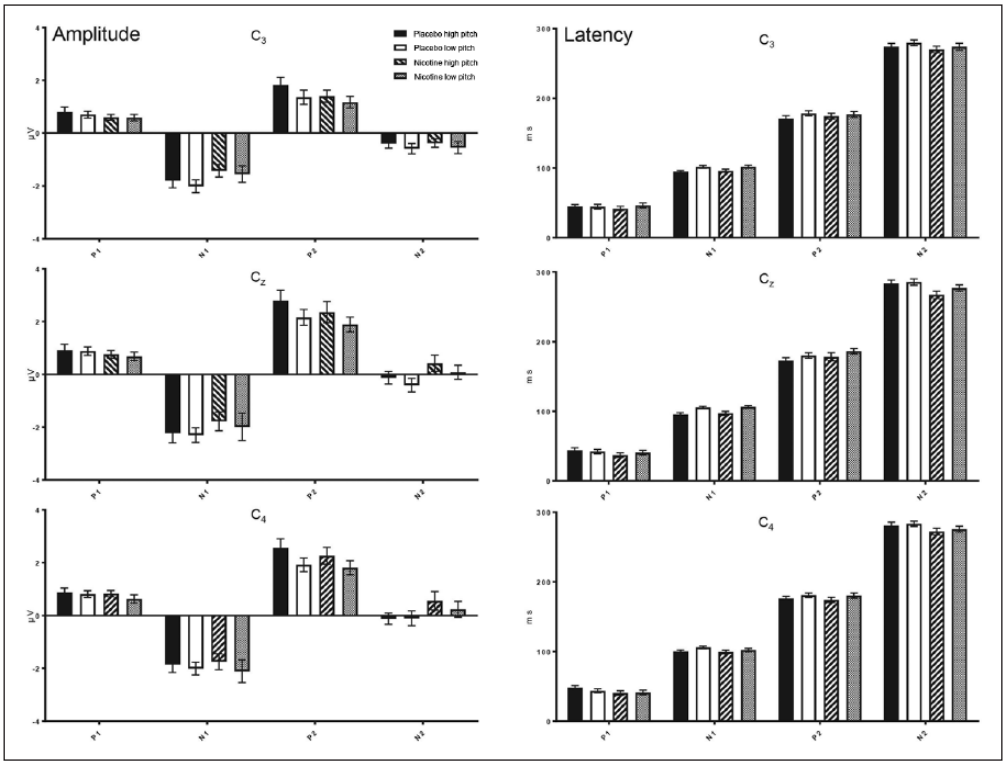


Figure 6. Amplitude (group mean values (mean ± SE) in μV) and latency (in milliseconds; ms) of Event-Related Potential (ERP) peaks in the central region, for the nicotine and placebo groups across the two pitch conditions (high and low). Note: P1, N1, P2 and N2 are ERP components; C_3, C_z, C_4 are electrode groups.

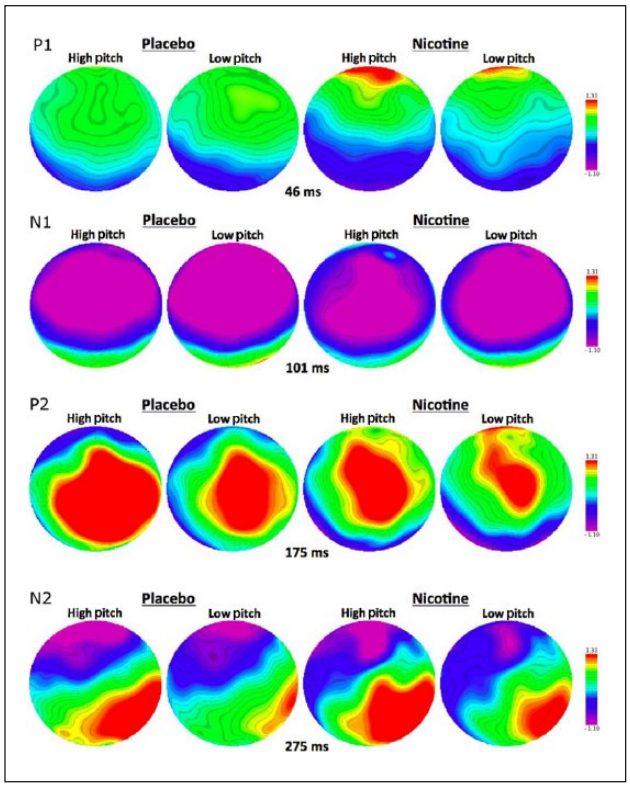


Figure 7. Topographic Event-Related Potential maps for the four components of interest at peak amplitude. P1: activation map captured at 46 ms for all pitch and drug conditions; N1: activation map captured at 101 ms for all pitch and drug conditions; P2: activation map captured at 175 ms for all pitch and drug conditions; N2: activation map captured at 275 ms for all pitch and drug conditions. All images are shown from an overhead viewpoint.

drug group, $F(2,58) = 3.59$, $p = 0.034$, $\eta^2 = 0.11$. However, post-hoc tests revealed no significant differences between drug groups in N1 amplitude at C_3, $F(1,30) = 1.43$, $p = 0.24$, C_z, $F(1,30) = 0.52$, $p = 0.48$, or C_4, $F(1,30) = 0.00$, $p = 1.00$.

For the N1 latency in the frontal region, there was a main effect of pitch, $F(1,28) = 18.81$, $p = 0.000$, $\eta^2 = 0.40$. High pitch had a significantly shorter N1 latency ($M = 97.96$, SEM = 1.67) than low pitch ($M = -104.04$, SEM = 1.29). There was also a main effect of area, $F(2,56) = 4.22$, $p = 0.020$, $\eta^2 = 0.13$, where N1 at F_4 was marginally significantly longer in latency ($M = 102.94$, SEM = 1.47) than both F_z ($M = 100.60$, SEM = 1.52), $p = 0.052$, and F_3 ($M = 99.47$, SEM = 1.49), $p = 0.05$. For N1 latency in the central region, there was a main effect of pitch, $F(1,29) = 24.59$, $p = 0.000$, $\eta^2 = 0.46$. High pitch ($M = 96.97$, SEM = 1.48) had a significantly shorter N1 latency than low pitch ($M = 103.52$, SEM = 1.08). There was also a main effect of area, $F(1.34,38.98) = 4.66$, $p = 0.03$, $\eta^2 = 0.14$, where N1 at C_3 had a significantly shorter latency ($M = 98.10$, SEM = 1.20) than at C_z ($M = 100.77$, SEM = 1.24), $p = 0.02$. Lastly, there was a significant interaction of pitch and area, $F(2,58) = 3.27$, $p = 0.045$, $\eta^2 = 0.10$. For all areas, high pitch had a shorter latency than low pitch. Specifically, for C_3, high pitch had a shorter N1 latency ($M = 95.48$, SEM = 1.37) than low pitch ($M = 101.69$, SEM = 1.38), $p = 0.00$. For C_z, high pitch had a shorter N1 latency ($M = 96.03$, SEM = 2.04) than low pitch ($M = 105.48$, SEM = 1.22), $p = 0.00$. For C_4, high pitch had a shorter latency ($M = 99.69$, SEM = 1.79) than low pitch ($M = 104.18$, SEM = 1.56), $p = 0.01$.

In summary, for N1 amplitude, the frontal region showed a main effect of pitch, with low pitch having a significantly larger N1 amplitude than high pitch, whereas the central region showed a main effect of area, with N1 amplitude at C_z being larger than at C_3. For N1 latency, both the frontal and central regions showed a main effect of pitch, with high pitch having a shorter N1 latency than low pitch (see Figures 4–7). Again, nicotine did not affect N1 amplitude or latency.

P2. For P2 amplitude in the frontal region, there was a main effect of drug group, $F(1,23) = 4.46$, $p = 0.046$, $\eta^2 = 0.16$. The nicotine group had a significantly larger P2 amplitude ($M = 1.68$, SEM = 0.25) than the placebo group ($M = 0.97$, SEM = 0.23). For the P2 amplitude in the central region, there was a main effect of pitch, $F(1,28) = 10.46$, $p = 0.003$, $\eta^2 = 0.27$. High pitch had a significantly larger P2 amplitude ($M = 2.03$, SEM = 0.17) than low pitch ($M = 1.62$, SEM = 0.15). There was also a main effect of area, $F(1.49,41.69) = 10.17$, $p = 0.001$, $\eta^2 = 0.27$, where P2 amplitude at C_3 ($M = 1.47$, SEM= 0.17) was significantly smaller than at both C_z ($M = 2.07$, SEM = 0.17), $p = 0.000$, and C_4 ($M = 1.94$, SEM = 0.16), $p = 0.04$.

For P2 latency in the frontal region, there was a main effect of pitch, $F(1,23) = 14.42$, $p = 0.01$, $\eta^2 = 0.39$, where high pitch had a significantly shorter P2 latency ($M = 168.49$, SEM = 3.43) than low pitch ($M = 178.87$, SEM = 3.30). For P2 latency in the central region there was a main effect of pitch, $F(1,28) = 8.26$, $p = 0.008$, $\eta^2 = 0.23$, where high pitch also had a significantly shorter P2 latency ($M = 174.04$, SEM = 2.76) than low pitch ($M = 180.39$, SEM = 2.35).

In summary, for P2 amplitude, the frontal region showed a main effect of drug group, with P2 amplitude being higher in the nicotine group for all conditions and areas compared with placebo (see Figures 4–7). The central region showed a main effect of pitch and area, with P2 amplitude being larger centrally during high pitch for both nicotine and placebo groups. For P2 latency, both the frontal and central regions showed a main effect of pitch, with high pitch having a shorter latency than low pitch for all areas.

N2. For N2 amplitude in the frontal region, there was a main effect of area, $F(1.39,24.93) = 6.69$, $p = 0.01$, $\eta^2 = 0.27$, where N2 amplitude at F_z was significantly larger ($M = -1.61$, SEM = 0.25) than at F_4 ($M = -1.14$, SEM = 0.18), $p = 0.00$. For N2 amplitude in the central region, there was a main effect of area, $F(1.49,40.30) = 10.08$, $p = 0.01$, $\eta^2 = 0.27$, where N2 amplitude at C_3 was significantly larger ($M = -0.40$, SEM = 0.11) than at both C_z ($M = -0.10$, SEM = 0.16), $p = 0.02$, and C_4 ($M = -0.80$, SEM = 0.17), $p = 0.01$.

For N2 latency in the frontal region, there was a main effect of area, $F(2,34) = 3.36$, $p < 0.05$, $\eta^2 = 0.17$, where N2 latency at F_4 was significantly shorter ($M = 266.56$, SEM = 3.08) than at F_z ($M = 272.41$, SEM = 3.64), $p = 0.03$. For N2 latency in the central region there were no significant findings.

In summary, for N2 amplitude, the frontal and central regions both showed main effects of area. For N2 latency, only the frontal region showed a significant effect, with the latency at F_4 being

significantly shorter (see Figures 4–7). Again, nicotine did not affect N2 amplitude or latency.

Discussion

The present study was designed to explore the potential cognitive mechanisms behind the co-consumption of nicotine and music. To this end, electrophysiological responses to high pitch and low pitch auditory stimuli were compared in groups of non-smoking participants receiving nicotine and placebo. The results indicate a relatively selective effect of nicotine on one particular component of auditory perception (P2, see below). However, effects of interest in relation to other aspects of auditory perception (P1, N1 and N2) were also noted within the task. These various components of auditory perception will be considered in turn.

P1

An increase in P1 amplitude as well as a decrease in P1 latency is thought to be indicative of enhanced arousal, which leads to improved primary auditory pathway transmission (Harkrider and Champlin, 2001; Le Houezec et al., 1994) and increased sensitivity to sensory input (Knott, 1985b). However, although nicotine does increase physiological (and self-reported) indices of arousal (Foulds et al., 1997), this was not reflected in a changed P1 amplitude or latency in the present study (although P1 amplitude was higher overall in the midline areas of the frontal and central regions of the scalp – F_z and C_z, consistent with previous research showing the auditory P1 to have maximal amplitude over these areas; Key et al., 2005). Although some previous research has found nicotine to increase P1 amplitude in smokers (Knott, 1985b) and non-smokers (Harkrider and Champlin, 2001), the effect overall has been weak and inconsistent across studies (Friedman and Meares, 1980). As a consequence, the present results and those of others reinforce the idea that arousal can be subdivided (Stavarache et al., 2009), and suggest that nicotine-induced arousal does not affect auditory processing, nor thereby as a corollary auditory transmission, or sensitivity to auditory stimuli in non-smokers.

N1

An increase in N1 amplitude is indicative of an enhancement of selective attention (Hillyard et al., 1973), while a decrease in N1 latency is related to more efficient information processing of stimuli (Domino and Kishimoto, 2002; Friedman et al., 1974a). However, in common with other nicotine studies with non-smokers (Harkrider and Champlin, 2001; Knott et al., 2009a, 2009b), nicotine did not affect the amplitude or latency of N1 in the present study, suggesting that for non-smoking populations, nicotine may not affect selective attention. That aside, pitch was shown to affect N1 amplitude and latency. That is, low pitch sounds resulted in a larger N1 amplitude compared with high pitch sounds in the frontal area. This contrasts with previous research showing N1 amplitude to increase for high pitch (Domino and Kishimoto, 2002) and high intensity sounds (Knott, 1985b). However, the results of these previous studies were observed with abstaining smokers, which suggests that non-smokers may react to auditory stimuli differently from smokers. Furthermore, responses to high pitch sounds in our non-smokers were found to have shorter N1 latencies compared with low pitch sounds in both the frontal and central regions. Interestingly, a previous study has found a similar result for abstaining smokers, but not for non-smokers (Domino and Kishimoto, 2002). This suggests there to be a more efficient processing for high pitch sounds compared with low-pitched sounds.

P2

A decrease in P2 amplitude is related to habituation processes (Ritter et al., 1968; Rust, 1977) and an enhanced ability to disengage from irrelevant stimuli (Knott, 1985a, 1989) indicative of more efficient processing (Domino and Kishimoto, 2002). Indeed, habituation can be considered an overlearning based on repetition that results in an increase in processing efficiency (Baldeweg et al., 2006). Our finding of a nicotine-induced increase in P2 amplitude in the frontal region suggests that in non-smokers nicotine may cause a lack of habituation, resulting in non-smokers being less able to adapt to repeated stimuli. In previous studies, P2 has been found to consistently decrease as a result of nicotine in auditory tasks of selective attention in smokers (Friedman and Meares, 1980; Friedman et al., 1974a, 1974b).

In the central region, P2 amplitude was found to be larger for high pitch compared with low-pitched stimuli. Harkrider and Champlin (2001) similarly found P2–N2 amplitude to increase for non-smokers with high-intensity stimuli compared with low-intensity stimuli. This suggests that high pitch sounds may be difficult to habituate to. High pitch sounds of equivalent intensity are physiologically louder than low pitch sounds (International Organization for Standardization, 2003). Knott (1985b) suggests that high intensity sounds may be difficult to ignore because they override selective mechanisms. Hence, they may also override other attentional processes as well, such as habituation, and therefore increase P2 amplitude.

For P2 latency, both the frontal and central regions showed a shorter latency for high pitch compared with low pitch sounds. Similar findings were reported by Domino and Kishimoto (2002), who found an increase in P2 amplitude as a result of irrelevant, high pitch tones. These results may suggest that high pitch sounds are processed faster than low pitch sounds, and therefore processed more efficiently.

With a lack of effect of nicotine on N1 amplitude, N1 latency and P2 latency, and with an increase in P2 amplitude in the frontal region, the results of this study contradict the most consistent findings of past research, which is that nicotine enhances selective attention and habituation processes. Our results suggest that non-smokers experience no change in selective attention and experience decrements in stimulus filtering and habituation processes as a result of nicotine intake (although it has to be acknowledged that selective attention was not assessed directly). This discrepancy may relate to the different stimuli (complex tones of different pitch) employed in our study and earlier studies (pulses, clicks and pure tones). Complex tones mimic natural sounds more closely and they are known to be processed differently at the neural level, as evidenced by electrophysiological and behavioural indices (Tervaniemi et al., 2000a, 2000b). However, perhaps more likely is the possibility that the effects of nicotine on selective attention and habituation in previous studies are more a reflection of withdrawal reversal, which

returns abstaining smokers' cognition to baseline, rather than genuine and absolute cognitive enhancement.

N2

The N2 component is inversely related to arousal (Picton and Hillyard, 1974; Picton et al., 1974) and therefore is reduced during states of high activation (Knott, 1989). Perhaps not surprisingly, given the negative results for P1 (which is also affected by arousal), N2 component amplitude and latency were not affected by nicotine in the present study. This contrasts with studies by Friedman and Meares (1980) and Friedman and colleagues (1974b), who report a nicotine-induced decrease in N2. Our findings, however, do accord with those of Knott (1985b) and Knott et al. (1995), both of whom used non-smokers, in contrast to Friedman and Meares (1980) and Friedman and colleagues (1974b), who both used smokers. This pattern of results suggests that previously reported effects of nicotine on N2 may relate to the reversal of withdrawal effects.

In conclusion, the results indicate a relatively selective effect of nicotine on one particular component of auditory perception, namely P2. The increase seen in P2 amplitude, indicating a decrease in habituation as a result of nicotine, suggests that people may smoke and listen to music at the same time because they do not experience a drop in emotional responses music when consuming nicotine. That is, music is repetitive by nature (Huron, 2006; Margulis, 2012) and past research has shown that familiarity with music, which is achieved through repetition, is a critical factor for emotional engagement with music (Pereira et al., 2011). Therefore, nicotine may help to stop smokers or other nicotine consumers from disengaging from music's repetitive elements by decreasing habituation. This is turn may lead to more emotional engagement with music during nicotine consumption. By decreasing adaptation, nicotine may extend the temporal window during which the listener is able to appreciate a piece of music rather than become bored with it.

Limitations and future research

Although sound stimuli of different pitches (as used in the present study) incorporate a fundamental musical dimension, they are of course not music. A simple definition of music is difficult to achieve; however, in addition to pitch, music also often contains rhythm and melody. These elements of music are extended in time and so are not suitable for investigation using an ERP paradigm. Future work could consider looking at responses to true musical excerpts – containing rhythm and melody – using fMRI, the signals for which evolve on a longer time scale than their electrophysiological correlates in the EEG.

Cigarettes are falling out of fashion thanks to the popularized electronic cigarette (e-cigarette) (Loughead, 2015). E-cigarettes work by inhalation of a heated liquid that usually contains nicotine and flavouring, as well as propylene glycol and glycerol (McRobbie et al., 2014). In this case, future experiments may be interested in using this method of nicotine administration because it most accurately imitates the act of smoking a real cigarette. This would increase the ecological validity for nicotine studies using a cigarette-smoking population. Furthermore, the growing popularity of e-cigarettes means that there is a part of the smoking population using this method of delivery in everyday life. For this reason, future experiments may also be interested in examining the cohort of smokers who use e-cigarettes compared with those who use tobacco products. E-cigarette users may respond differently to nicotine since e-cigarettes deliver the drug at a much slower and lower rate than regular cigarettes, which can result in lower absorption of the drug (Farsalinos et al., 2014; Schroeder and Hoffman, 2014). This difference in delivery and absorption may lead to different cognitive and electrophysiological responses and may ultimately affect consumers' preferences for certain nicotine products.

Finally, the present study was confined to non-smokers. It is likely that smokers' response to nicotine would be different from that of non-smokers, due (for example) to pharmacokinetic and pharmacodynamic tolerance (e.g. Porchet et al., 1988). Therefore, further research could consider a design that compares the effects of nicotine on auditory processing in smokers and non-smokers.

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