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Nicotine and smoker status moderate brain electric and mood activation induced by ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist

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Abstract

As the increased smoking prevalence in schizophrenics may be interpreted as an adaptive response to an underlying biological defect, investigations into nicotine's actions within *N*-methyl-D-aspartate (NMDA) antagonist drug models of schizophrenia may improve our understanding of the role of glutamatergic neurotransmission in initiating and maintaining nicotine dependence in this disorder. In this double-blind, placebo-controlled, randomized study, the electroencephalographic (EEG) and subjective response to a sub-psychotomimetic intravenous dose of the NMDA antagonist ketamine was examined in 20 regular smokers and 20 non-smokers pretreated with placebo or nicotine gum. Although nicotine increased EEG arousal, ketamine produced electrocerebral signs of brain activation (decreased slow wave power) and sedation (decreased fast wave power and frequency), which were not affected by nicotine pretreatment and were evident only in non-smokers. Ketamine increased a number of self-report indices of subjective arousal, some of which were attenuated and potentiated by nicotine in smokers and non-smokers, respectively. These findings suggest that long-term (evidenced by smoker vs. non-smoker comparisons) and short-term (acute) nicotine exposure may alter NMDA receptor-mediated arousal and mood systems in a way that promotes nicotine dependence in smokers, and addresses neurobiological deficiencies in smokers with schizophrenia.

Keywords: Smokers; Non-smokers; Nicotine; Nicotine dependence; Glutamate; *N*-methyl-D-aspartate; Electroencephalography; Mood; Schizophrenia

1. Introduction

Restrictive regulations and public education campaigns have dramatically diminished community rates of smoking from ~60% to ~25% over the past four decades. There is growing evidence, however, that smoking is becoming increasingly concentrated in highly dependent and vulnerable, at-risk populations (Glassman, 1993) which over-include people of lower socio-economic status and individuals with other drug dependencies and/or behavioral or affective deficits amenable to management by nicotine (Pomerleau, 1997). Nicotine dependence (ND) is inordinately high in psychiatric patients, this population being the heaviest smokers and comprising ~44% of the tobacco market (Lasser et al., 2000).

There is a particularly high percentage of smokers (~49–92%) in the schizophrenic (vs. mood disorder) population (de Leon and Diaz, 2005; Hughes et al., 1986) who, compared to non-patient smokers, perceive more benefits and find cigarettes more appealing than alternative rewards (Spring et al., 2003). Smoking has been shown to be a predictive factor in the onset of schizophrenia (Weiser et al., 2004) as well as a protective factor (Zammit et al., 2003), and has been shown to be heaviest in the more impaired schizophrenics (Apud et al., 2000) and for individuals currently receiving treatment (de Leon, 1996), which suggests that, in some cases, heavy smoking might be a form of self-medication of cognitive/affective deficits, and/or of neuroleptic

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side effects (Levin et al., 1996). Given nicotine's mood-elevating actions in non-patient and patient populations (Kalman, 2002; Salin-Pascual, 2002), and its brain activational effects, indexed by cerebral blood flow (Rose et al., 2003; Zubieta et al., 2001) and metabolic rate (Domino et al., 2004a,b; Stapleton et al., 2003) in a number of sub-cortical and fronto-cortical structures regulating arousal, emotion and reward states, schizophrenic patients may smoke, in part, to alleviate negative symptoms (e.g., apathy, blunted affect, anhedonia, social withdrawal) which have been associated with dopamine (DA) deficiency and metabolic hypofrontality (Chambers et al., 2001; Watkins et al., 2000; Ziedonis and George, 1997). The neurobiological mechanism underlying the putative heightened reward value of smoking in both patients and non-patients is believed to involve acetylcholine (ACh) and DA, with nicotine activating nicotinic cholinergic receptors (nAChRs) on DA neurons in the ventral tegmental area (VTA) of the mesocorticolimbic reward pathway, resulting in increased DA release in both the nucleus accumbens (NAcc) and prefrontal cortex (Dani and De Biasi, 2001; Davis et al., 1996; Watkins et al., 2000).

Although dopaminergic systems play an important role in arousal, cognitive and motor functions, it is recognized that nicotine-mediated nAChR stimulation of these systems precipitates a complex participation with other neurotransmitters (including norepinephrine [NE], serotonin [5-HT], gamma-aminobutyric acid [GABA], and glutamate [Glu]) affecting upstream and downstream targets and processes associated with reward and motivation (Dani and De Biasi, 2001; Mansvelder et al., 2003; Watkins et al., 2000). The excitatory amino acid neurotransmitter Glu, important in cortico–cortical and cortical–subcortical interactions, is particularly relevant here, as observations of abnormal CSF levels and postmortem receptor binding in some, but not all studies, have implicated a Glu deficiency in schizophrenia (Konradi and Heckers, 2003; Moghaddam, 2003; Ohnuma et al., 2005). Preclinical studies have observed acute nicotine to activate pre-synaptic nAChRs on glutamatergic terminals, resulting in an increased evoked release of Glu (Gray et al., 1996; McGhee et al., 1995; Pidoplichko et al., 2004) which in turn, excites the NMDA (*N*-methyl-D-aspartate) subtype of Glu receptor on VTA DA neurons, leading to increased neuronal burst firing and release of DA in the NAcc (Hu and White, 1996; Kalivas et al., 1993). Conversely, blockade and antagonism of NMDA receptors has been found to block nicotine-induced DA release in the NAcc (Schilstrom et al., 1998; Sziraki et al., 1998).

Support for NMDA involvement in schizophrenia is evidenced by reduced cortical and sub-cortical NMDA receptor densities (Deakin et al., 1989; Simpson et al., 1992) and reduced NMDA-induced Glu release in synaptosomal fractions prepared from schizophrenic postmortem brains (Sherman et al., 1991). Moreover, whereas treatment with a partial agonist of the NMDA receptor (*d*-cycloserine) has been found to reduce negative symptoms in medication-free schizophrenic patients (van Berckel et al., 1998), acute single doses of the NMDA antagonist phencyclidine (PCP) can exacerbate previously presented schizophrenic positive symptoms in stabilized patients (Ban et al., 1961; Luby et al., 1962). These observations have led to proposals for NMDA antagonists to be used as a pharmacological model for schizophrenia, and a considerable number of study paradigms involving brief (~1 h) steady-state infusions of subanesthetic doses of ketamine, a PCP derivative with less potent but similar effects in preclinical paradigms (Rothman and Olney, 1987), have induced transient and reversible schizophrenic-like positive (e.g., hallucinations, delusions, thought disorders) and negative symptoms, as well as changes in mood and cognition (in attentional, mnemonic, and learning domains) in healthy volunteers (Adler et al., 1998; Krystal et al., 1994; Malhotra et al., 1996; Newcomer et al., 1999). Ketamine has also rekindled core psychotic symptoms and has induced cognitive impairments in patients with schizophrenia (Ban et al., 1961; Lahti et al., 1995; Luby et al., 1999; Malhotra et al., 1997). Functional neuroimaging methodologies have implicated multiple brain regions responsible for NMDA-mediated psychosis, with psychctomimetic doses of ketamine resulting in hyperactivation of frontal/pre-frontal and parietal cortices, as well as the anterior cingulate, putamen, and caudate nucleus (Breier et al., 1997; Fu et al., 2005; Honey et al., 2004; Lahti et al., 1995; Rowland et al., 2005; Vollenweider et al., 1997a,b, 2000). Infrahuman electrophysiological and neurochemical investigations with ketamine have found, along with increased levels of extracellular levels of Glu in the NAcc, depressed synaptic transmission between the NAcc and hippocampus (Hunt et al., 2005) but enhanced synaptic efficacy between the NAcc and both the basolateral amygdala (Kessal et al., 2005) and prefrontal cortex (Razoux et al., 2006).

Theoretically, acute and chronic nicotine exposure may alter the neurobehavioural response to ketamine by acting on one or more neurotransmitter systems shown to interact with NMDA receptor systems (Domino et al., 2004a,b; Krystal et al., 1998, 1999). The current study, assessing the interactive effects of nicotine and a subanaesthetic dose of ketamine in a placebo-controlled double-blind design, was intended to provide preliminary objective data for the formulation of testable hypotheses concerning the interaction of nicotine — Glu relationships in the regulation of brain activation and mood states which may be implicated in schizophrenia and/or in reinforcement processes underlying ND in vulnerable individuals. Although lacking the spatial resolution of functional neuroimaging strategies, the non-invasive nature and superior temporal resolution of electroencephalography (EEG) make it a suitable tool for probing activational patterns, particularly as it has proven sensitive to acute and chronic dosing with multiple classes of psychotropic agents (Knott, 2000). Spectral EEGs have repeatedly portrayed a stimulant-like (Knott, 1990) electrocerebral activation pattern (increased fast [alpha$_2$, beta] and decreased slow wave [delta, theta, alpha$_1$] activity) with acute smoking/nicotine (Knott, 1988, 1989a,b, 1991a,b, 1995, 1997, 2001; Knott et al., 1995; Lindgren et al., 1999), which contrasts with the increased slow wave and diminished alpha activity seen in schizophrenia (Knott et al., 2001) and the general cortical EEG slowing evidenced with ketamine treatment (Mandema and Danhof, 1992; Marquis et al., 1989; Popoli et al., 1990; Schüttler et al., 1987). In this study, nicotine will be examined acutely, by administering a single dose of nicotine polacrilex, and chronically, by comparing smokers and non-smokers. As it remains unclear as to whether ketamine-induced effects on activational and affective states

reflect the direct effects of ketamine or are secondary to ketamine-induced schizophrenia-like psychosis, the present study administered a low, non-psychotomimetic dose of ketamine. As a secondary objective, gender differences were also examined, as males generally appear to be more sensitive to nicotine (Benowitz and Hatsukami, 1998; Perkins, 1997; Perkins et al., 1999).

2. Method

2.1. Subjects

Healthy, right-handed male ($n=20$) and female ($n=20$) volunteers were recruited using local advertisements at universities and in local newspapers. Half of the males and females were non-smokers and the remaining half were smokers. For inclusion, non-smokers had to report smoking no more than a lifetime total of 5 cigarettes (none in the past year), and smokers had to be smoking a minimum of 15 cigarettes per day for at least the past 5 years. All potential participants underwent a semi-structured screening for psychiatric disorders (including alcohol/drug abuse) and for general health, and were also assessed with the Family Interview for Genetic Studies (Nurnberger et al., 1994) in order to rule out relevant psychopathology within first-degree relatives. Screening also included a physical examination involving an electrocardiogram and routine laboratory tests (complete blood count, routine blood chemistry, urine analysis and a urine toxicology for drug use). In addition, handedness was determined using the Edinburgh Inventory handedness scale (Oldfield, 1971); current life stress was rated with the Severity of Psychosocial Stressors Scale (SPSC-A) for Adults (American Psychiatric Association, 1994), and vulnerability to psychosis was assessed with the Bell Reality Testing Inventory (BRTI: Bell, 1991) and the Perceptual Aberration Subscale (PAS) of the Wisconsin Psychosis Proneness Scale (Chapman et al., 1982). Smokers were also administered the Fagerstrom Tolerance Questionnaire (FTQ) as indicator of the degree of nicotine dependence (Fagerstrom, 1978).

None of the volunteers reported a personal or first-degree family psychiatric history or a serious medical illness, and none exhibited abnormal results on physical examination and laboratory testing. All were within normal limits on measures of current life stress and psychosis vulnerability. Demographic and smoking characteristics of the groups are shown in Table 1. No significant group differences were observed with any of the measures and smokers were rated on the FTQ as being moderately dependent on nicotine.

The study was approved by the Research Ethics Board of the Royal Ottawa Health Care Group and all volunteers signed an informed consent prior to study participation.

2.2. Design

Volunteers participated in four test sessions within a double-blind, placebo-controlled crossover design with four parallel groups, including male smokers, female smokers, male non-smokers, and female non-smokers. Two of the four test sessions involved intravenous infusion of ketamine and in the remaining two sessions participants were infused with a placebo. Also, in one of the ketamine and placebo infusion sessions, volunteers were pretreated with nicotine, and in the other two sessions they were pretreated with a matching nicotine placebo. Order of the four sessions (placebo–placebo, placebo–ketamine, nicotine–placebo, nicotine–ketamine) was counterbalanced and sessions were separated by a minimum one-day interval.

Table 1
Mean (±S.E) characteristics of participants

	Non-smoker	Non-smoker	Smoker	Smoker
	Female	Male	Female	Male
Age	22±1.1	21.7±1.2	22.9±1.4	23.2±1.2
No. years smoking	NA	NA	8.05±1.5	7.55±0.8
Cigs. smoked per day	NA	NA	13.85±2.0	19.7±3.5
Nicotine yield (mg) per cig.	NA	NA	1.07 – 2.94	0.98 – 2.43
FTQ score[a]	NA	NA	5.3±0.6	4.8±0.7

[a] Fagerstrom Tolerance Questionnaire: above FTQ scores (which can range from 0–11) indicate a moderate level of dependence.

2.3. Procedures

For each of the four test sessions, volunteers arrived at the laboratory (8:00 a.m.) following overnight (beginning 12:00 a.m.) abstinence from food, drugs, alcohol and caffeine. Smokers also abstained from smoking for the same period of time and their abstinence was verified by expired air carbon monoxide (CO) readings, which were required to be below 15 parts per million (ppm). Following EEG electrode placement and the insertion of an antecubital intravenous line, volunteers rested for a 45-min adaptation period and then dynamic baseline assessments of EEG and subjective ratings were collected over a 24-min period. Volunteers were then administered either active or placebo nicotine, and, after a 30-min administration/absorption period, ketamine or placebo infusion was initiated simultaneously with a second administration of the dynamic test battery. At the completion of each dynamic battery, volunteers completed additional subjective rating instruments not included in the battery.

2.4. Drugs

Nicotine was administered in the form of nicotine polacrilex, a specifically formulated drug product that permits controlled release of nicotine upon chewing, providing delivery primarily *via* buccal absorption (Hukkanen et al., 2005). A 4 mg Nicorette Plus (Hoechst Roussell) gum piece or matching placebo (same size, colour and texture as active gum) was chewed (with nose plugs, so as to reduce any possible sensory impact differences between nicotine and placebo) over a 25-min period according to manufacturer guidelines, with participants using an audiotape to instruct them to bite the gum twice per minute and to "park" the gum (i.e. inside the mouth) between bites. An additional 5-min absorption period, involving the chewing of a strong mint gum to help disguise any placebo vs. nicotine flavor differences, followed the gum chewing so that the subsequent

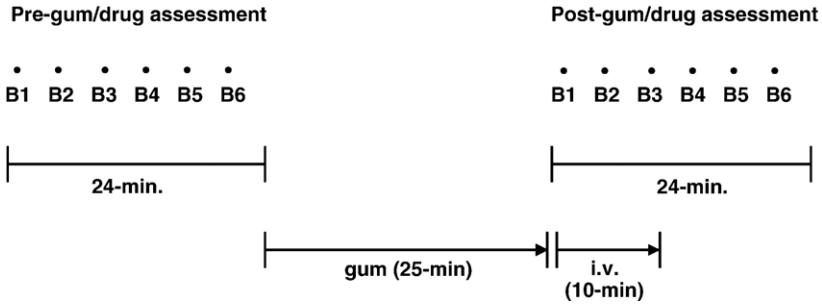

Fig. 1. Schematic time-line for the six assessments (B1–B2) carried out at baseline (pre-gum/drug) and after post-gum/drug administration.

infusion of ketamine coincided with maximum (T_{max} ~ 30-min) blood nicotine concentrations, which were expected to range between 10–17 ng/ml (Hukkanen et al., 2005).

Schizophrenia-like symptoms have been consistently induced with acute systemic infusions of ketamine doses well below those (1–2 mg/kg) used in human anesthesia, either by administering a constant dose (.5 mg/kg) over a ~60-min period (Krystal et al., 1994), or by administering an initial bolus (Malhotra et al., 1996) or loading dose (Newcomer et al., 1999), both followed by infusion of a maintenance dose of ketamine to achieve steady state ketamine blood levels over a ~60-min period. As loading doses of 0.27 mg/kg and 0.08 mg/kg have produced marked and mild psychotomimetic-like reactions, respectively, with no subjective effects or measurable plasma ketamine levels being observed with 0.024 mg/kg (Newcomer et al., 1999), this study utilized an intermediate low loading dose of 0.04 mg/kg, but no maintenance dose, with the aim of avoiding schizophrenia-like symptoms. An automated pump apparatus (Imed Gemini PC-1) infused 0.04 mg/kg ketamine hydrochloride or placebo (saline [0.9% sodium chloride] solution) over a 10-min period in order to maximize safety.

2.5. Assessments

EEG and mood measures were collected in a dynamic manner by repeated assessments in the form of six successive 2-min time blocks, each block separated by a 2-min period (Fig. 1). For each of the six 2-min blocks in the 24-min duration battery, the initial 90-s was used to acquire EEG and the remaining 30-s of each six blocks was used to assess mood status.

2.5.1. EEG measures

Eyes-closed, vigilance-controlled, monopolar (linked-ear reference) electrical activity was sampled at 512 Hz (amplifier bandpass settings of 0.1–40.0 Hz) from 21 electrode (impedance < 5 κΩ) scalp sites (Fp_z, Fp_1, Fp_2, F_z, F_3, F_4, F_7, F_8, C_z, C_3, C_4, T_3, T_4, T_5, T_6, P_z, P_3, P_4, O_z, O_1, O_2). Electro-oculographic (EOG) activity was recorded with electrodes placed on the supra-orbital ridge and external canthus of one eye. A minimum of fifteen 2-s duration artifact-free epochs were submitted to Fast Fourier Transform (FFT) analysis to compute, at each scalp site, average (across the 15 epochs) power (μV^2) of delta (1.5–4.0 Hz), theta (4.0–8.0 Hz), total alpha (8.0–13.0 Hz), sub-$alpha_1$ (8.0–10.5 Hz), sub-$alpha_2$ (10.5–13.0 Hz) and beta (13.0–30.0 Hz)

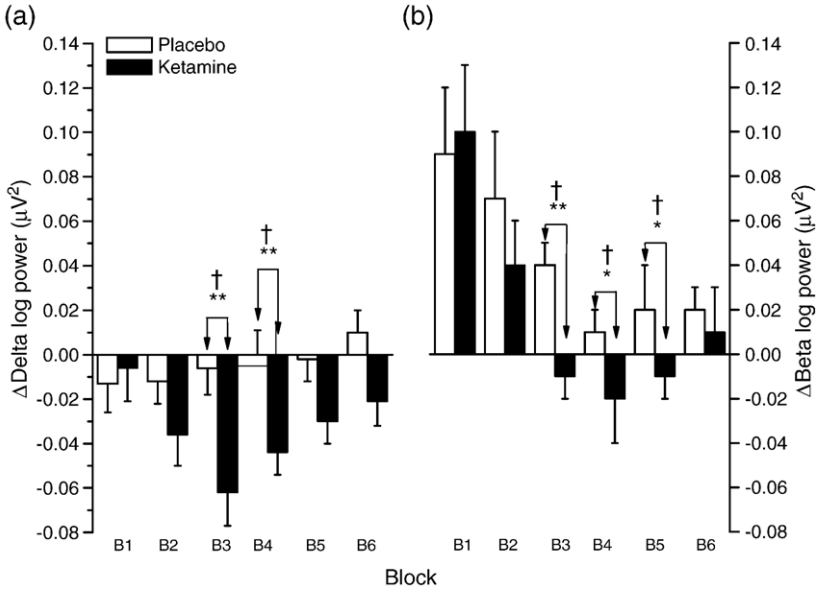

Fig. 2. Bars represent mean (±S.E.) delta (panel "a") and beta (panel "b") log power changes (post-drug/placebo values minus mean baseline value) associated with placebo (▭) and ketamine (▬) across time blocks. *Significant difference for placebo vs. ketamine treatment comparisons, $p < .01$. †Significant difference for within ketamine treatment comparisons; blocks 3 and 4 significantly different from blocks 1, 5, and 6, $p < .05$.

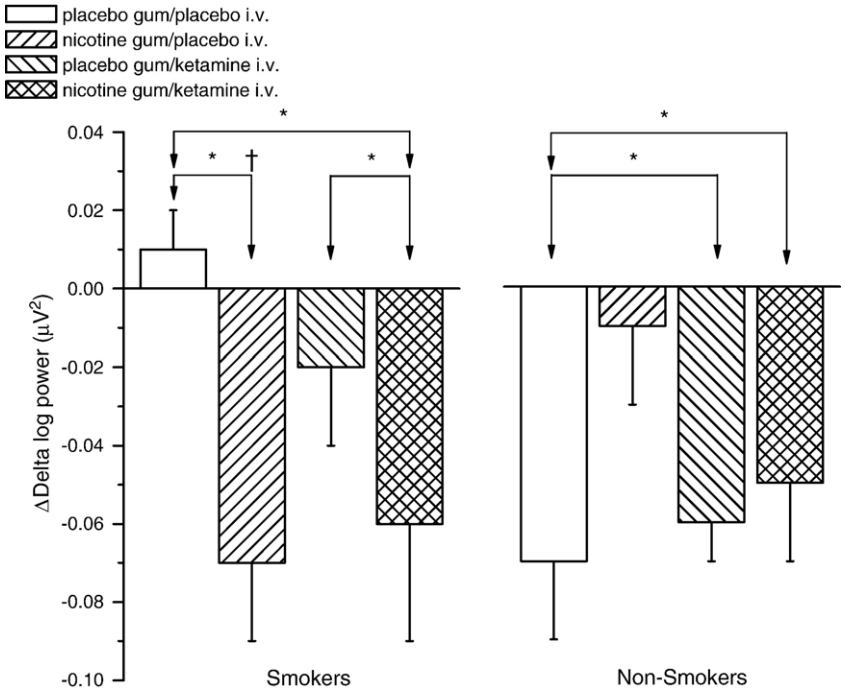

Fig. 3. Bars represent mean (±S.E.) delta log power changes (post-drug/gum values minus mean pre-drug/gum values) induced by separate and combined administration of nicotine and ketamine in smokers and non-smokers (collapsed over gender and time blocks). Conditions include: placebo infusion preceded by placebo gum (▭), placebo infusion preceded by nicotine gum (▨), ketamine infusion preceded by placebo gum (▧), and ketamine infusion preceded by nicotine gum (▩). *Significant treatment difference, $p<.01$. †Significant between-group (smokers vs. non-smokers) difference, $p<.05$.

frequency bands. Band power values were log-transformed in order to approximate normal distributions (Gasser et al., 1982). Peak frequency was also computed for each of the four main frequency bands, with peak frequency being calculated as the frequency bin within each band exhibiting the maximum power.

2.5.2. Mood ratings

In the last 30-s of each of the six 2-min assessment blocks, volunteers were prompted by audio taped recordings of 6 affect descriptors (each separated by ~4-s) including "stimulated", "head rush", "relaxed", "alert", "jittery" and "dizzy". These items

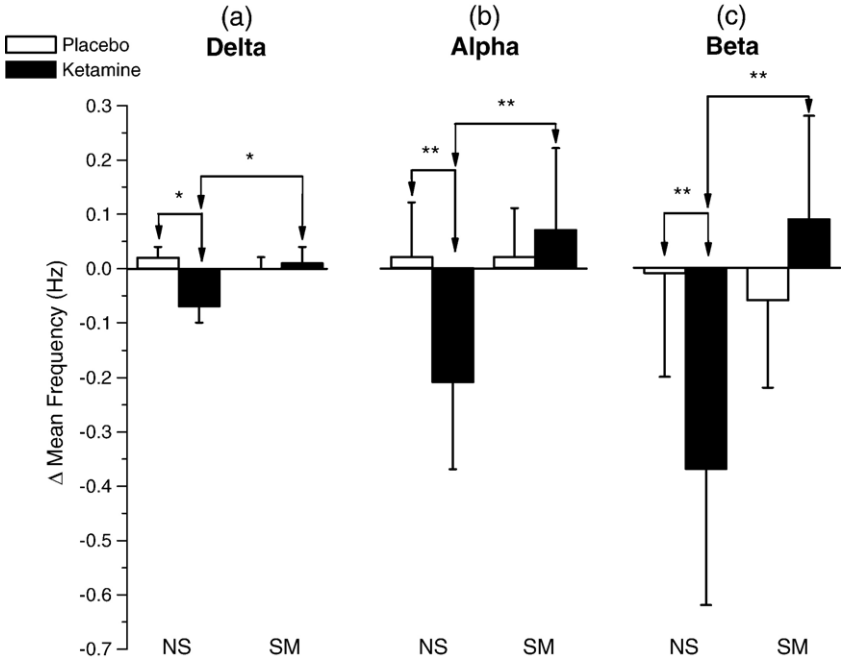

Fig. 4. Bars represent mean (±S.E.) delta (panel a), alpha (panel b) and beta (panel c) frequency changes (post-drug/placebo values minus mean pre-drug/placebo values) induced by placebo (▭) and ketamine (■) infusions (collapsed over gender, gum conditions and blocks) in smokers (SM) and non-smokers (NS). *,**Significant differences, $p<.05$ and $p<.01$, respectively.

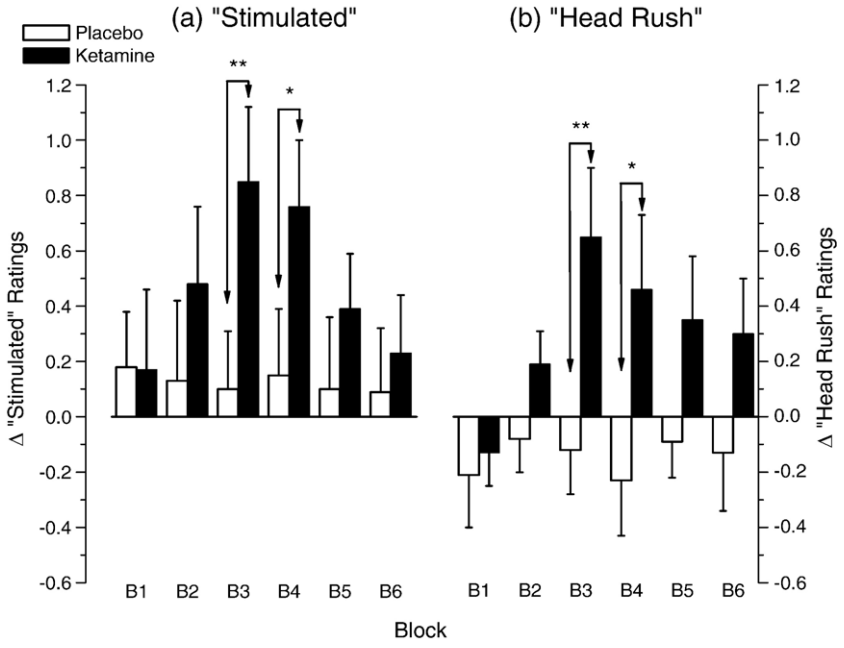

Fig. 5. Bars represent mean (±S.E.) "stimulated" and "head rush" rating changes (post-drug/placebo values minus mean pre-drug/placebo baseline values) associated with placebo (▭) and ketamine (▬) infusions (collapsed over all groups, and gum conditions) across time blocks. *,**Significantly different, $p<.05$ and $p<.01$, respectively.

have been shown to be sensitive to smoking, as well as to the positive and negative affects resulting from nicotine being administered to smokers and non-smokers, respectively (Heishman et al., 1993). Volunteers were instructed to verbally respond to each descriptor by calling out a number on a 10-point scale from 0 ("not at all") to 10 ("very much").

At completion of the first and second test battery, mood was further assessed with the "arousal" sub-scale of the Stress-Arousal Checklist (SACL) (Mackay et al., 1978). The scale required participants to rate 15 adjectives (e.g. energetic, vigorous, lively etc.) on a 4-point scale ('0' [definitely do not feel] to '3' [definitely feel]), the scale values being summed to form a single SACL-arousal score.

2.5.3. Drug effects

Two additional items adapted from the Heishman et al. (1993) desire–strength questionnaire (DSQ) were used to gauge the participant's feelings towards the drug/gum and required them to rate on a visual analog scale, how strong the drug effect was (scale ranging from 0 [definitely a blank] to +2 [extremely strong]) and how strong was their desire to have another dose like they just had (scale ranging from −2 [strongly resist] to +2 [strongly desire]). With this latter static rating scale, volunteers were instructed to complete the ratings with respect to their general feelings experienced throughout the previous (post-drug/gum) 24-min assessment period.

2.5.4. Vital signs

Heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure were assessed as safety measures with an automated vital signs monitor (Dinamap Pro Model 1000) at the end of baseline, following gum chewing, and again after the post-gum/drug assessment.

2.6. Analysis

Each baseline EEG and mood measure was subjected to separate univariate analysis of variance (ANOVA) procedures with time block (×6) acting as a repeated measures factor and smoker status (×2) and gender (×2) acting as between-group factors. To assess the separate and combined net effects of nicotine and ketamine, EEG and mood measures collected during the baseline battery were averaged across the six 2-min time points and the resulting mean values were subtracted from values derived from each (non-averaged) of the six individual block values of the second battery. Each of the derived EEG and mood change scores were subjected to separate ANOVA procedures, with drug (×2), gum (×2) and time block (×6) serving as repeated-measures factors, and smoker status (×2) and gender (×2) acting as between-group factors. For both sets of analyses, scalp site was also entered as a within-treatment factor. Change scores were also derived for the static mood measures, SACL-arousal and DSQ, which were subjected to similar ANOVAs but with no time block factor. Greenhouse–Geisser corrections were applied where appropriate to compensate for violations of sphericity assumed with univariate ANOVAs. Significant ($p<.05$) main or interaction effects were followed up with Bonferroni-adjusted pairwise comparisons. To reduce the number of follow-up comparisons and the potential for Type I statistical errors, significant electrode site effects were not followed up unless they interacted with drug, gum or gender.

3. Results

None of the 40 volunteers reported adverse effects with either ketamine or nicotine administration, and no psychotomimetic

experiences were reported in the two ketamine sessions. Analysis of baseline values failed to yield any significant main or interaction effects for mood ratings. Similarly, EEG analysis evidenced no significant effects except for electrode site for alpha, alpha$_1$ and alpha$_2$ power measures which, on visual inspection, exhibited the expected posterior>anterior scalp power gradient. The analysis of change scores resulted in significant main and interaction effects for EEG and mood as described below.

3.1. EEG measures

For delta, a significant drug (F=7.8, df=1/35, p<.01) and a drug×time interaction (F=3.3, df=5/175, p<.01) found ketamine reduced power (M=−.03, SE+.005) relative to placebo infusion (M=− .006, SE=.007) and, as shown in Fig. 2, this power reduction, although peaking at block 3, was significantly different from placebo both at block 3 and at block 4. Within the ketamine treatment, delta power in blocks 3 and 4 was significantly attenuated compared to power in blocks 1, 5 and 6. A significant effect of gum (F=7.3, df=1/35, p<.01) showed nicotine gum attenuated delta power (M=− .037, SE=.009) compared to placebo gum (M=− .002, SE=.008). Follow-up of a drug×gum×smoker interaction (F=9.9, df=1/35, p<.004) found nicotine-induced delta reductions in smokers but not in non-smokers, and whereas in non-smokers ketamine produced delta reductions which were not affected by nicotine pretreatment, ketamine alone failed to reduce delta in smokers and delta reductions with ketamine following nicotine pretreatment were no different from that seen with nicotine pretreatment alone (Fig. 3).

Analyses of theta power yielded a significant drug effect (F=4.7, df=1/35, p<.05) with ketamine resulting in a slight

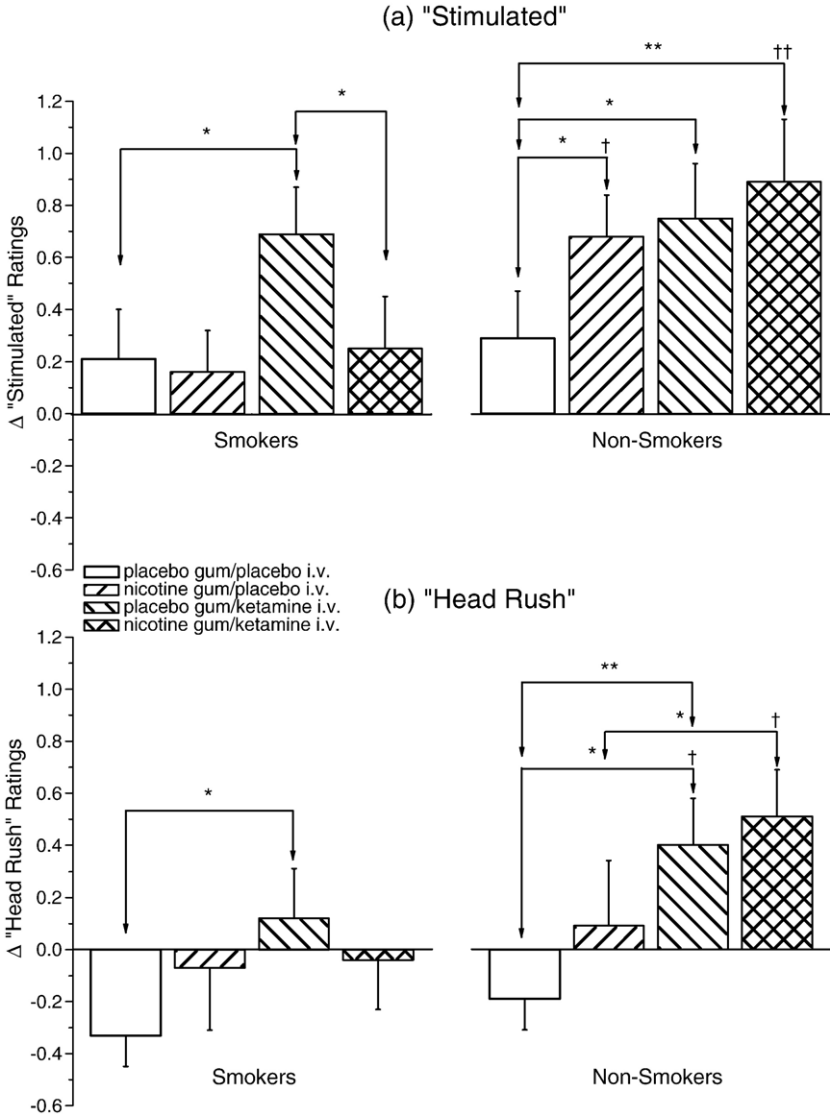

Fig. 6. Bars represent mean (±S.E.) "stimulated" and "head rush" changes (post-drug/gum values minus pre-drug/gum mean baseline values) ratings induced by ketamine and nicotine in smokers and non-smokers (collapsed over gender and time blocks). Drug conditions include placebo infusion preceded by placebo gum (▭), placebo infusion preceded by nicotine gum (▨), ketamine infusion preceded by placebo gum (▧), ketamine infusion preceded by nicotine gum (▩). *,**Significant treatment difference, p<.05 and p<.01, respectively. †,††Significant between-group (smokers vs. non-smokers) differences, p<.05 and p<.01, respectively.

reduction in power ($M=-.01$, SE=.008) relative to placebo infusion ($M=.02$, SE=.010). A significant effect of gum ($F=8.0$, $df=1/35$, $p<.008$) found that nicotine attenuated theta ($M=-.02$, SE=.01) compared to placebo gum ($M=.02$ Hz, SE=.09). No significant main or interaction effects were observed with power in total alpha or the two sub-alpha bands, but a significant drug × time interaction ($F=3.1$, $df=5/175$, $p<.02$) found ketamine infusion to reduce beta at blocks 3, 4 and 5 compared to placebo infusion (Fig. 2). Within ketamine treatment, beta power in blocks 3–5 were significantly reduced compared to power in blocks 1 and 2.

Frequency analysis yielded a significant gum × smoker effect ($F=4.3$, $df=1/35$, $p<.05$), with nicotine gum slowing ($p<.05$) delta frequency ($M=-.17$ Hz, SE=.03) compared to placebo gum ($M=.01$ Hz, SE=.02) in smokers but not in non-smokers (placebo gum: $M=-.01$ Hz, SE=.02; nicotine gum: $M=-.02$, SE=.03). Follow-up of drug × smoker interaction ($F=4.8$, $df=1/35$, $p<.04$) showed the delta slowing induced by ketamine to be evidenced only in non-smokers (Fig. 4). As with delta, a gum × smoker interaction ($F=6.7$, $df=1/35$, $p<.01$) showed nicotine ($M=-.10$ Hz, SE=.04) but not placebo ($M=-.01$ Hz, SE=.05), to slow theta frequency, but only in smokers. Frequency in the total alpha band also exhibited a gum × smoker interaction ($F=5.8$, $df=1/35$, $p<.02$), with frequency acceleration being seen only in smokers following nicotine gum ($M=0.23$ Hz, SE=.13) versus placebo gum ($M=0.05$ Hz, SE=.07). In addition, total alpha band frequency exhibited a drug × smoker interaction ($F=5.4$, $df=1/35$, $p<.03$), with follow-up comparisons evidencing a slowing in this band with ketamine which was limited to non-smokers (Fig. 4). A gum × smoker interaction ($F=8.0$, $df=1/35$, $p<.01$) for beta frequency showed frequency in this band to be increased with nicotine gum ($M=0.54$ Hz, SE=.22) compared to placebo gum ($M=0.16$ Hz, SE=.13) in smokers but not in non-smokers (placebo gum: $M=.09$ Hz, SE=.23; nicotine gum: $M=.16$ Hz, SE=.21). Follow-up of a significant drug × smoker effect ($F=6.3$, $df=1/35$, $p<.02$) found that relative to placebo infusion, infusion with ketamine decreased beta frequency but only in non-smokers (Fig. 4).

3.2. Mood ratings

Analysis of mood changes dynamically assessed during each of the six blocks of the test battery failed to find any alterations with "alert", or "relaxed" affect descriptors, but significant main and/or interaction effects were observed with the remaining four adjectives. For "stimulated", follow-up a significant drug ($F=9.2$, $df=1/35$, $p<.004$) and drug × time ($F=3.7$, $df=5/175$, $p<.03$) effect found that compared to placebo infusion, ketamine increased ratings at blocks 3 and 4 (Fig. 5). A gum × smoker interaction ($F=4.7$, $df=1/35$, $p<.04$) showed a stimulating effect ($p<.05$) for nicotine ($M=.64$, SE=.15) compared to placebo ($M=.28$, SE=.15) in non-smokers but not in smokers (placebo: $M=.28$, SE=.16, nicotine: $M=.23$, SE=.16). Follow-up comparisons of a drug × gum × smoker interaction ($F=8.6$, $df=1/35$, $p<.01$) found ketamine to increase ratings of stimulation only in smokers and only with placebo gum pretreatment, the effect being antagonized with nicotine pretreatment (Fig. 6). In contrast, nicotine, ketamine, and nicotine and ketamine combined all increased stimulated ratings in non-smokers. Between-group comparisons showed that ratings of stimulation with nicotine in non-smokers were greater than those seen with nicotine in smokers ($p<.05$) as were ratings with nicotine and ketamine combined ($p<.01$).

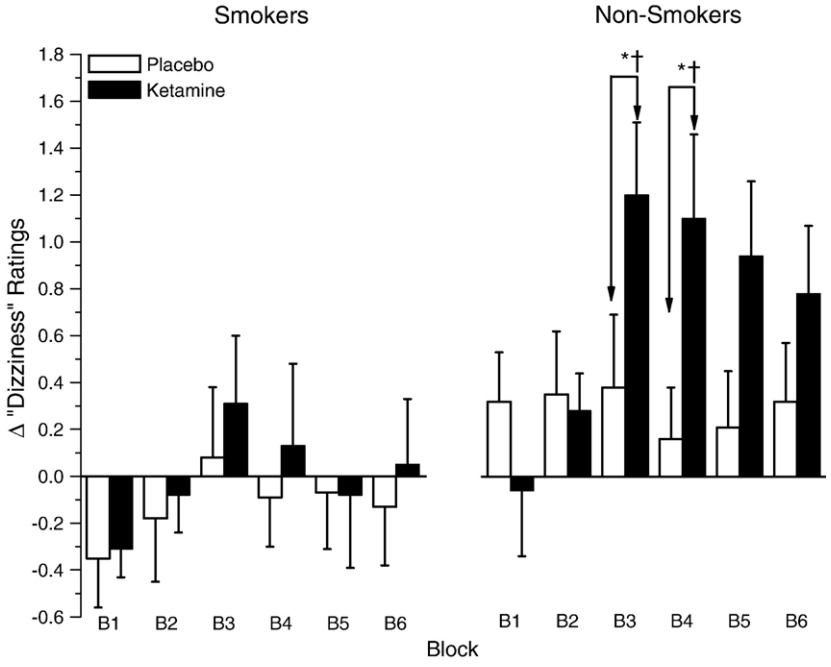

Fig. 7. Bars represent mean (±S.E.) "dizzy" rating changes (post-placebo/drug values minus mean pre-placebo/drug baseline values) induced by placebo (▭) and ketamine (▬) infusions in smokers and non-smokers (collapsed over gender and gum conditions). *Significant block difference, $p>.05$. †Significant between-group (smokers vs. non-smokers), $p<.05$.

Analysis of a drug × gender effect ($F=7.7$, $df=1/35$, $p<.01$) found that relative to placebo infusion ($M=.73$, SE=.16), ketamine infusion reduced ($p<.05$) subjective stimulation ($M=.38$, SE=.15) in females but increased stimulation in males (placebo: $M=.24$, SE=.17; ketamine: $M=.59$, SE=.16).

"Head rush" ratings also exhibited significant drug ($F=9.6$, $df=1/35$, $p<.004$), and drug × block ($F=3.0$, $df=5/175$, $p<.03$) effects, analysis of which showed ketamine infusion to produce higher ratings than placebo infusion at blocks 3 and 4 (Fig. 5). As with "stimulated" ratings, a drug × gum × smoker interaction ($F=5.8$, $df=1/35$, $p<.03$) found that relative to placebo infusion, only ketamine infusion resulted in modest, but significant increases in rush ratings in smokers, while in non-smokers, ketamine pretreated with both placebo and nicotine gum increased ratings, with ketamine-induced rating increases being greater ($p<.05$) in non-smokers than in smokers (Fig. 6). Nicotine did not increase rush ratings.

Follow-up of a drug × time × smoker interaction ($F=3.3$, $df=5/175$, $p<.04$) showed ketamine to induce greater subjective "dizziness" than placebo infusion at blocks 3 and 4, but only in non-smokers (Fig. 7). Between-group comparisons also showed these ketamine-altered dizziness ratings to be greater in non-smokers than smokers ($p<.05$). Analysis of "jittery" ratings yielded a drug × gum interaction ($F=3.9$, $df=1/35$, $p<.05$), where nicotine pretreatment prevented the ketamine-induced rating reductions seen with ketamine alone in both smokers and non-smokers ($p<.05$).

Analysis of a gum × smoker ($F=4.4$, $df=1/35$, $p<.04$) effect for SACL ratings found that relative to placebo ($M=.65$, SE=1.1), nicotine gum ($M=4.5$, SE=1.4) increased ($p<.01$) subjective arousal in non-smokers but not in smokers (placebo: $M=2.8$, SE=1.1; nicotine: $M=2.3$, SE=1.4). A drug × gender interaction ($F=5.3$, $df=1/35$, $p<.03$) saw increased ($p<.05$) arousal with ketamine infusion ($M=4.8$, SE=1.8) compared to

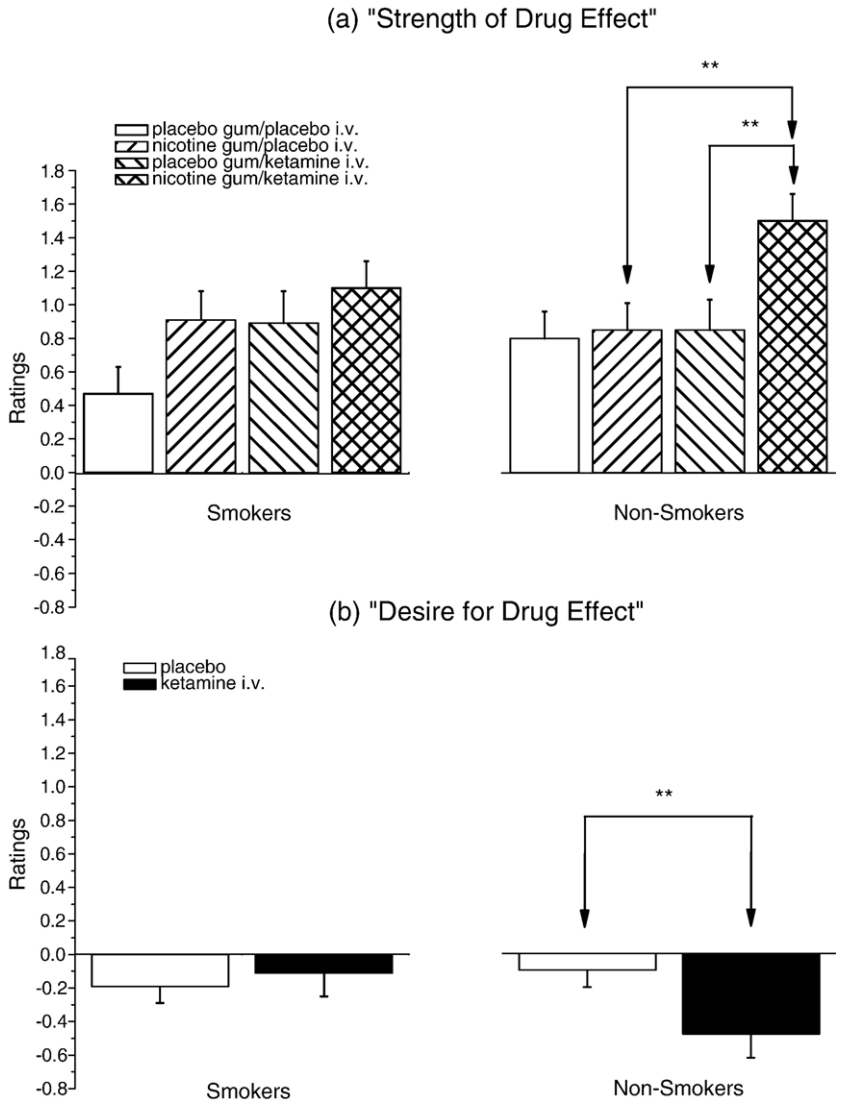

Fig. 8. Bars represent mean (±S.E.) subjective effects of drug/gum on ratings of "strength of drug effect" (panel a) and "desire for drug effect" (panel b). Drug conditions for panel (a) includes placebo infusion preceded by placebo gum (▭), placebo infusion preceded by nicotine gum (▨), ketamine infusion preceded by placebo gum (▨), ketamine infusion preceded by nicotine gum (▩). Drug conditions for panel (b) include placebo i.v. (▭) and ketamine i.v. (collapsed across gum condition (■)). *Significantly different, $p<.05$.

placebo infusion (M=1.7, SE=1.3) to be evidenced in females but not in males (placebo infusion: M=1.1, SE=1.2; ketamine infusion: M=3.2, SE=1.2).

3.3. Drug effects

One male smoker inappropriately completed the DSQ ratings and his data was not included in the analysis. Ratings for 'strength of drug effect' showed a significant gum (F=8.2, df=1/35, p<.01), drug (F=6.6, df=1/35, p<.02) and a drug×gum×smoker interaction (F=5.9, df=1/35, p<.01). Ratings overall were greater for nicotine (M=1.1, SE=.09) than for placebo gum (M=0.8, SE=.09), and for ketamine (M=1.1, SE=.11) than for placebo i.v. (M=0.8, SE=.09), but only in non-smokers did nicotine and ketamine interact, with nicotine pretreatment of ketamine resulting in greater ratings than with nicotine or ketamine alone (Fig. 8a). Analysis of the 'desire for drug effect' ratings found a significant drug×smoker interaction (F=7.8, df=1/35, p<.01) with only the non-smokers showing a greater desire for a ketamine effect than for a placebo i.v. effect (Fig. 8b).

3.4. Vital signs

Technical problems with the automated monitor resulted in missing vital signs for n=6 smokers and n=1 non-smoker. A drug×gum interaction (F=4.2, df=1/28, p<.05) found significant (p<.05) increases in heart rate only when ketamine infusion was pretreated with nicotine gum (M=4.2 bpm, SE=1.8) compared to placebo gum (M=1.3 bpm, SE=1.9). Drug×gender (F=4.7, df=1/28, p<.04) and drug×smoker (F=4.7, df=1.28, p<.04) interactions saw significant (p<.04) increases in SBP with ketamine (M=2.5 mm Hg, SE=1.2) compared to placebo infusion (M=− .88 mm Hg, SE=1.2) in males, as well as significant increases (p<.04) in non-smokers with ketamine (M=2.2 mm Hg, SE=1.5) compared to placebo infusion (M=−1.2 mm Hg, SE=1.1). Follow-up of a drug×gum interaction (F=5.9, df=1/28, p<.02) showed nicotine gum (M=3.4 mm Hg, SE=.5) to elicit significant (p<.04) increases in DBP compared to placebo gum (M=1.6 mm Hg, SE=.7) only in the presence of placebo infusion. Analysis of a gum effect (F=4.8, df=1/28, p<.04) found that nicotine gum (M=5.4 mm Hg, SE=.9) increased DBP compared to placebo gum (M=.3 mm Hg, SE=.9).

4. Discussion

The significantly greater incidence of smoking in schizophrenia than in depression implicates diagnostic specificity, which might reflect schizophrenia's unique pathophysiology (Spring et al., 2003). Examining nicotine's impact on transient disruption of NMDA receptor function in healthy volunteers is a useful strategy for laboratory investigations attempting to understand the role of glutamatergic neurotransmission in the relationship between schizophrenia and ND. By combining EEG and dynamic/static self-rating probes, the present study assessed in non-patients the effects of nicotine and smoking status on brain and mood activation changes resulting from brief systemic exposure to a non-psychotogenic dose of ketamine. Ketamine, particularly at peak infusion, produced electrocortical signs both of activation and de-activation, as shown by power reductions in slow (delta, theta) and fast (beta) waves, respectively. While nicotine in smokers also resulted in electrocerebral arousal as evidenced by power reductions in delta and theta and decreases and increases in slow and fast frequencies, respectively. One of the principal findings of this study was that the ketamine-induced delta neuroactivation response was observed only in non-smokers, and was not altered by nicotine pretreatment. Mood effects were evident with the separate and combined administration of ketamine and nicotine, but of particular relevance to this investigation was the observation that ketamine-induced increases in several dynamically assessed self-reported arousal indices were seen in both smokers and non-smokers but were differentially potentiated or antagonized by nicotine pretreatment, either selectively ("stimulated" and "head rush") or non-selectively ("jittery") in the two smoker groups. The failure to find any of these ketamine or interaction effects to vary with gender suggests that nicotine's effect on glutamatergic neurotransmission, although perhaps interacting with menstrual cycle, may not be relevant to the different motivational systems underlying the initiation and maintenance of female and male smoking behaviour.

Although these findings of electrocerebral and subjective activation were elicited with a subdissociative dose of ketamine, and were not accompanied by psychotomimetic experiences (e.g. perceptual abnormalities and reality distortions), they are in line with previous reportings of increased cortical/subcortical hemodynamic and metabolic resting state activity and euphoric and manic-related aspects of ketamine-induced psychosis (Vollenweider et al., 2000) which, as in our study, have also been accompanied by self-reports of dizziness, lightheadedness, exhilaration and "high" (Krystal et al., 1994; Morgan et al., 2004; Newcomer et al., 1999; van Berckel et al., 1998). The paradox of evoking hyperarousal states by blocking an excitatory receptor suggests that relatively low doses of the non-competitive antagonist ketamine produce a net activational effect. While the exact neuronal mechanisms underlying this functional activation are yet unclear, pharmacological rodent models (Olney et al., 1999; Rujescu et al, 2006) suggest that the core mechanism involves NMDA receptor blockade triggering an inactivation of GABA neurons and consequent disinhibition of excitatory pathways, resulting in excessive release of excitatory transmitters, including Glu (Moghaddam et al., 1997) and ACh (Kim et al., 1999), and DA (Coyle, 1996, 2004; Coyle et al., 2003). Psychotomimetic responses to subanesthetic doses of ketamine are proposed to result from the augmented activity of these excitatory pathways that converge to hyperstimulate non-NMDA and catecholaminergic neurotransmitters from corticolimbic neurons. Although this may well involve DA systems, the ability: (a) of the opiate antagonist naltrexone to enhance the psychotic-like response to a subperceptual dose of ketamine (Krystal et al., 2006), and (b) of the atypical antipsychotic clozapine, but not of the typical antipsychotic drug haloperidol, to block ketamine-induced brain metabolic activation (Duncan et al., 2000) and to suppress

the emergence of psychotomimetic symptoms with ketamine (Malhotra et al., 1997), may indicate that receptor systems other than DA D_2 are implicated in the complex neural and behavioural responses resulting from NMDA hypofunction.

The neuroelectric actions induced with the subanaesthetic dose of ketamine appear to contrast with the initial characteristic EEG changes associated with anaesthetic ketamine doses (Marquis et al., 1989; Popoli et al., 1990; Schüttler et al., 1987), which can be described by 3 sequential phases, including: loss of 6–14 Hz alpha together with a reduction in overall EEG amplitude and a decrease in mean frequency (phase I); appearance of a persistent rhythmic large amplitude (4–6 Hz) theta rhythm (phase II), and with high doses, the emergence of an intermittent polymorphic (0.5–2.5 Hz) delta (phase III). Nicotine pretreatment did not alter EEG or the electrocortical response to ketamine in non-smokers, but nicotine itself did activate the EEG in smokers, albeit to a lesser extent than that typically seen with smoke-inhaled or intravenous nicotine which, as in the current study, not only slow alpha frequency and decrease slow (delta, theta) wave power, but also increase fast (alpha, beta) wave power in non-patient smokers (Knott, 2001; Lindgren et al., 1999) and in patients with schizophrenia (Knott et al., 1995). As with our present findings, the topographic distribution of smoking/nicotine-induced EEG power changes have generally been reported to be diffuse (Domino et al., 1992) but scalp regional differences involving hemispheric asymmetry or frontal regions have been observed (Knott et al., 1998a,b), the latter effects varying with nicotine dose (Domino et al., 1995; Knott, 1989a,b) and efficiency of frontal lobe executive functions in healthy volunteers (Knott et al., 1995), and with clinical ratings of positive and negative symptoms in schizophrenia (Knott et al., 1995). Although the selective EEG response to nicotine in smokers in this study may involve altered nervous system functioning resulting from chronic smoke exposure, it also supports contentions that vulnerability to ND is related to individual differences in sensitivity to nicotine (Perkins, 1995; Pomerleau et al., 1993). Similarly, diminished neuroelectric responsivity to ketamine in smokers vs. nonsmokers may be attributed to constitutional/genetic factors or may result from neuroadaptive alterations in the glutamatergic system related to chronic smoking. To date, the study of Glu system alterations related to smoker status have been limited to gene expression of NMDA post synaptic receptor density (PSD), with a number of NMDA-PSD genes exhibiting increased expression in all smokers vs. non-smokers, and several being selectively elevated only in schizophrenic smokers vs. schizophrenic non-smokers (Mexal et al., 2005). That chronic smoking significantly dampens neuroelectric responsivity to ketamine, perhaps due to the impact of NMDA molecular changes on downstream functioning of GluU signaling pathways, suggests that ND in schizophrenia may be motivated in part by altered symptomatology resulting from neuroadaptions in the NMDA system. These symptom changes may involve motivational systems as well as cognitive processes as chronic nicotine administration in rats increases the expression of the ionotropic Glu receptor subunit 2/3 (GluR2/3) in the VTA, but also of NMDA receptor subunits 2A (NR2A) and NR2B in the prefrontal cortex (Wang et al., 2006). Although not nicotine related, it is important to point out that the smokers vs. non-smoker differences in EEG responsivity to placebo (Fig. 3), which may reflect individual differences in adaptation or emotional response to the experimental conditions.

Given that: (a) nAChRs are the primary site of action of nicotine; (b) delta activity is regulated primarily by nAChR-enriched subcortical centers (Riekkinen et al., 1991); (c) delta reductions induced by nicotine are prevented by pretreatment with the nAChR antagonist mecamylamine but not with muscarinic or dopaminergic (DA D_2) antagonist treatments (Knott et al., 1998a,b; Walker et al., 2001), nor with serotonergic-depleting (Perugini et al., 2003) or alpha-2-noradrenergic agonist treatments (Knott et al., 2005); and (d) intracellular electrophysioligical experiments have revealed excitation of cortical post-synaptic potentials to be regulated in part by nAChRs located on glutamatergic efferent terminals (Vidal, 1994), it is not unreasonable to suggest that the differential impact of smoker status on ketamine- and nicotine-induced slow wave EEG responsivity may also reflect neuroadaptive changes in nAChRs sensitivity resulting from chronic nicotine exposure. In regular smokers, repeated smoking throughout the day causes a cycling of conformational changes in these receptors, through resting, activated (following rapid puff-delivered nicotine boli), desensitized (with sustained nicotine exposure) and inactivated states (Dani and De Biasi, 2001; Dani et al., 2001). Pharmacological magnetic resonance imaging (phMRI) of cerebral blood volume on drug-naive rats has shown acute functional activation of cortical and subcortical structures by nicotine to be mediated by $\propto 4\beta 2$-containing nAChRs, presumably belonging to the high affinity $\propto 4\beta 2$ nAChR subtype which is relatively abundant in the brain and is a high affinity target for nicotine (Gozzi et al., 2006). The upregulation in high affinity $\propto 4\beta 2$ nAChRs observed with chronic, long-term daily nicotine exposure, (Buisson and Bertrand, 2001) seen in regular smokers (Benwell et al., 1988), and to a lesser extent in schizophrenic smokers (Breese et al., 2000; Durany et al., 2000), has been thought to reflect a compensatory homeostatic response attributed to decreased receptor function (Buisson and Bertrand, 2002). Considering that, as in rodent models (Flores et al., 1997), the increase in high affinity receptor numbers in smokers is dose-dependent (i.e. correlated with cigarette packs per day) and is not related either to length of time smoked (Breese et al., 1997) or to neuroleptic treatment (Lee et al., 2001), the heavier smoking in schizophrenia may act to reduce $\propto 4\beta 2$ receptor sensitivity to the excessive ACh and the consequent neuroactivation resulting from NDMA hypofunction. These suggestions however are somewhat weakened by several reports of increased sensitivity of these $\propto 4\beta 2$ nAChRs with chronic nicotine treatment (Nashimi et al., 2003; Vallejo et al., 2005).

The self-reported "jittery" ratings which were increased with ketamine, were antagonized by nicotine pretreatment regardless of smoker status, but nicotine antagonism of ketamine-induced increases in 'stimulated' and 'head rush' ratings (more evident in non-smokers, as were nicotine's self-reported arousing experiences) was evident only in smokers, and nicotine potentiation of strength ratings of ketamine effects were seen only in non-smokers. Meta-analytic reviews of nicotine's subjective effects have noted marked differences between smokers and non-smokers in response to acutely administered nicotine, with variability between these groups varying with affective dimension as well as with nicotine dose and route of administration (Kalman and Smith, 2005). The

dissociation between nicotine's mood and EEG arousing properties in smokers, and nicotine's differential moderation of ketamine-associated subjective arousal in smokers and non-smokers, may be reflective of the singular or interacting roles of NMDA receptors and of ∝4β2-containing and ∝7-containing nAChRs in modulating physiologic and behavioural arousal, and the response uniqueness of these nAChR receptor subtypes to the acute agonist treatment when superimposed on non-smoking and chronic smoking histories. In general, schizophrenia is associated with diminished ∝7-nAChR expression in selected brain regions (Court et al., 1999; Freedman et al., 1995; Evan et al., 1999) and given their co-location on glutamatergic nerve terminals, their stimulation may impact on downstream stimulation of NMDA receptors as these low affinity ACh receptors regulate, in part, glutamate's calcium dependent release from presynaptic stores. Although brain nicotine concentrations achieved by most smokers have not significantly increased low affinity ∝7 receptors (Court et al., 1998; Breese et al., 2000), their numbers have been elevated in rodents, but at a higher nicotine concentration than that required for ∝4β2 receptor up-regulation (Marks et al., 1986). Given our current findings of the selective antagonism of ketamine's mood arousing actions in smokers by acutely administered nicotine, it is possible that acute and chronic smoking in schizophrenia may act in concert to address the issue of diminished ∝7-nAChRs and to attenuate the affective disturbances associated with aberrant NDMA receptor functions. This position has received partial support from the recent findings that anabasine, a selective nAChR agonist, attenuates behaviours elicited by NMDA antagonists in rats (Mastropaolo et al., 2004), and that nicotine, combined with the atypical antipsychotic clozapine (a cholinergic enhancer as well as serotonergic/dopaminergic blocker), attenuates schizophrenia-associated pre-attentive processing impairments induced with NDMA antagonism (Levin et al., 2005).

5. Limitations

The present study, considered a preliminary investigation into the moderating role of smoker status and acute nicotine on the neural and subjective effects of ketamine in normal healthy adults, had a number of limitations that need to be addressed in future research. First, at the subject level, sample sizes were relatively small and smokers were only moderately dependent on nicotine and were assessed after over-night smoking abstinence. Comparison of these smokers with more dependent smokers following both abstinent and non-abstinent states would shed light on the role of withdrawal processes in ketamine-nicotine interactions and would provide results more relevant to ND in schizophrenics who tend to be heavy smokers (Leonard et al., 2001). Second, only a single nicotine dose was employed and it was administered via nicotine polacrilex, a route that results in slow absorption and favours nAChR desensitization (Dani et al., 2001). Similarly, ketamine was administered as a single dose, and at a subpsychotogenic level, which makes it difficult to relate the present findings, to schizophrenia-associated psychopathophysiology evidenced with psychotomimetic doses of ketamine. Varying subjective effects have been observed with subperceptual vs. low perception-altering doses of ketamine (Krystal et al., 2006; Morgan et al., 2004), so the antagonistic and potentiating actions of nicotine observed in this study may differ quantitatively and qualitatively when examined with psychotomimetic ketamine dosing. In addition, the lack of a steady-state infusion condition, and the failure to measure plasma ketamine and nicotine levels (as well as their metabolites) over the session, prohibits strong conclusions regarding the pharmacodynamic time-response effects of these drugs. Finally, assessments were limited in number and scope, and affect measures were self-reported and did not include observer-rated assessments.

The clinical significance of these limited EEG and mood findings awaits further testing with psychotogenic doses of ketamine and clinical psychometric assessments of schizophrenia-associated symptomatology, preferably with nicotine administration routes (e.g. nasal inhaler or spray) which can mimic the rapid nicotine delivery provided by cigarette smoking. Given the numerous cognitive impairments reported with ketamine-induced NMDA hypofunction (Krystal et al., 1994; Malhotra et al., 1996; Morgan et al., 2006; Newcomer et al., 1999; Parwani et al., 2005), and nicotine's performance enhancing properties which have been documented in non-patients and schizophrenics (Depatie et al., 2002; George et al., 2002; Levin et al., 1996; Smith et al., 2006), these future efforts should include cognitive assessments across multiple domains, as well concurrent functional imaging probes so as to better localize the neuropathophysiology of glutamate-nicotine interactions underlying ND in schizophrenia, as well as to further our insight into the potential utility of glutamatergic and cholinergic treatments for schizophrenia (Stip et al., 2005; Tuominen et al., 2005;).

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