The effects of prolonged abstinence on the processing of smoking cues: an ERP study among smokers, ex-smokers and never-smokers

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in press: Journal of Psychopharmacology

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Acknowledgements

This work was supported by the Netherlands Organisation for Scientific Research (NWO).

Abstract

Processing bias is an important feature of substance abuse. The issue whether processing bias is a more or less permanent feature of nicotine addiction remains to be resolved. The present study addresses the role of smoking status on smoking-related processing bias. We employed Event-Related Brain Potentials (ERPs) as measure of processing bias to investigate this issue. Further, self-report measures of nicotine craving and pleasantness ratings of smoking stimuli were obtained. Three groups, smokers, ex-smokers and never-smokers, were compared on their electrophysiological brain response to smoking-related and neutral pictures. The present study shows that both the P300 and SPW amplitudes in response to smoking-related pictures are significantly more enhanced for smokers than for ex-smokers and never-smokers at frontal and central sites, whereas the magnitude of the P300 and SPW amplitudes in response to neutral pictures does not differ between the three groups. Accordingly, it can be concluded that smokers show more bias for smoking-related pictures than ex-smokers and smokers. Because there is no significant difference between the P300 and SPW amplitudes of ex-smokers and never-smokers, it can also be concluded that ex-smokers display the same (low) level of processing bias as never-smokers. In addition, nicotine-craving ratings and pleasantness ratings of smoking stimuli were higher in smokers compared to ex-smokers. It can be concluded that the smoking-related craving, pleasantness rating, and processing bias decreases after a period of prolonged abstinence.

Key-words: Smoking, nicotine, processing bias, event-related potentials

Introduction

Substance use disorders are associated with processing biases for drug-related stimuli (for reviews see Field et al., 2006; Franken, 2003). These processing biases are thought to emerge because of the motivational and attention-grabbing properties of drug cues (Robinson and Berridge, 1993). For drug-dependent persons these stimuli are extremely attractive, become the focus of attention, and are able to elicit approach behaviors such as drug seeking and drug consumption (Robinson and Berridge, 1993). The hyperattentive state of drug users that is associated with drugs and drug-related stimuli is called attentional bias. The incentive-sensitization theory of Robinson and Berridge (1993) provides an explanation for this bias in drug abuse patients. This theory predicts that repeated administration of drugs causes a sensitization of dopamine neurotransmission in the striatum, which in turn causes drugs and drug-associated stimuli to acquire incentive motivational properties. This 'incentive salience' or relevance of stimuli for reinforcement makes the drug-associated stimuli extremely 'wanted' and therefore a greater proportion of attentional resources is allocated to them. Further, because the neurobiological substrates of this wanting system are irreversibly sensitized, it is implicitly hypothesized that this enhanced processing does not decrease after abstinence. A related theoretical account of addiction is Franken's model of attentional bias (2003), in which it is speculated that the presence of attentional bias may increase drug-related cognitions, enhance the signaling of drug cues and diminish the attentional resources left for alternative cues, all of which in turn may strengthen the enhanced processing of drugs and drug-related stimuli. Furthermore, Franken's model predicts that craving is reciprocally associated with the attentional processing of drug-related stimuli.

That is, the presence of craving results in enhanced processing of drug-related stimuli and vice versa.

The clinical importance of this enhanced processing has been demonstrated in several studies that found a relation between relapse rates and performance on the emotional Stroop task, a measure of attentional bias. This relation has been demonstrated in smokers (Waters et al., 2003), alcoholics (Cox et al., 2002), cocaine (Carpenter et al., 2006), and heroin dependent subjects (Marissen et al., 2006). In a study using a visual probe task, this relation between relapse and processing bias was not observed (Waters et al., 2003), suggesting that only the Stroop task has predictive value.

Substance-related processing bias has been demonstrated in heroin (Franken et al., 2000; Lubman et al., 2000) and cocaine abusers (Hester et al., 2006) and heavy alcohol drinkers (Field et al., 2004; Townshend and Duka, 2001). In addition, also smokers exhibit this processing bias (Ehrman et al., 2002; Gross et al., 1993; Waters and Sayette, 2006). Processing bias for smoking-related stimuli is present in both light to moderate smokers (Waters and Feyerabend, 2000) and heavy smokers (Waters et al., 2003), and in both smokers who abstained from smoking for a couple of hours and smokers who recently smoked (Rusted et al., 2000). Lifetime consumption of nicotine and extent of smoking dependence appear unrelated to this bias (Waters and Feyerabend, 2000; Waters et al., 2003), but number of unsuccessful quitting attempts as well as attitudes against smoking appear to be respectively positively and negatively correlated (Bradley et al., 2003; Johnsen et al., 1997). However, some studies did not find a positive relationship between processing bias and indices of smoking behavior such as the number of cigarettes smoked per day (Hogarth et al., 2003; Hogarth et al., 2005; Mogg et al., 2005),

implicating that this relationship is far from clear and that more research on this topic is needed.

A relatively new approach to assess the processing of drug-related stimuli is the measurement of event-related potentials (ERP) using electroencephalography (EEG) techniques. The ERP consists of several time-locked components, all of which reflect one or more information-processing operations. The amplitude of the components presumably depicts the extent to which an information-processing operation is engaged (for reviews, see Coles et al., 1990; Gehring et al., 1992). ERP has several advantages above reaction time measurements. ERP methodology provides a potentially more direct assessment of processing bias than conventional reaction time data since brain activity can be measured directly without relying on motor-responses. Further, it is possible to derive some indications of neural generators. For example, it is known that early visual ERP components are associated with activity in the extrastriate cortex (e.g. Schupp et al., 2003), although of course, neuroimaging methodology such as fMRI is more suitable for this goal. In addition, ERP methodology is suitable to study the temporal dynamics of the processing. That is, early components of the ERP are thought to reflect the more automatic, stimulus-driven cortical processing of a stimulus, whereas later components most likely reflect more voluntary, top-down controlled processing (Carretié et al., 2004).

ERP research addressing the processing of drug-related stimuli show that the later ERP components, such as the P300 and the Slow Positive Wave (SPW), are enhanced in drug use populations, in contrast to earlier components and drug naïve populations (e.g. Franken et al., 2003). This is in line with behavioral data showing that processing biases are only found when stimuli are presented above the threshold of awareness, i.e. do not

operate in preconscious processes (Bradley et al., 2004; Franken et al., 2000; Mogg and Bradley, 2002).

Although there is still some debate on the exact meaning of these late components, it is widely believed that they reflect attentive processing as well as the activation of motivational and arousal systems in the brain (Cuthbert et al., 2000; Lang et al., 1997; Schupp et al., 2000). In recent ERP studies of addiction, it has been found that these late ERP components are adequate indices of the processing of drug-related stimuli (Franken et al., 2003; Van de Laar et al., 2004). More specifically, enhanced P300 and SPW amplitudes resulting from the processing of drug-related stimuli have been found in alcohol, cocaine, and heroin dependent patients (Franken et al., 2003; Herrmann et al., 2000; Herrmann et al., 2001; Namkoong et al., 2004; Van de Laar et al., 2004).

As for smokers, Warren and McDonough (1999) were the first to study processing biases using ERPs. In accordance with the results of aforementioned studies (e.g. Namkoong et al., 2004), they found significant ERP discrepancies between smoking-related and neutral pictures at the P412, a component similar to the P300. This discrepancy was significantly larger for smokers than for never-smokers at Fz and Cz electrodes, indexing enhanced processing of smoking-related stimuli. Never-smokers also showed a difference in P412 amplitude between smoking-related and neutral cues in this study, but the location of this difference was, in contrast to smokers, more posterior, being most pronounced at central and parietal-temporal sites. Additional analyses revealed that the effects for never-smokers were smaller than for smokers and therefore Warren and McDonough (1999) assume that their P300-like component indeed reflected the allocation of attentional resources toward information relevant to the smokers'

tobacco-addicted, incentive-motivational states. The effects found in never-smokers could have been due to task demands, arising from the realization that the study dealt with cigarette smoking. In contrast to cocaine and heroin-dependent patients (Franken et al., 2004; Franken et al., 2003; Van de Laar et al., 2004), Warren and McDonough did not observe significant differences between smokers and nonsmokers on the SPW component. Recently, Fehr et al. (in press) demonstrated an attentional bias in smokers for smoking related words compared to neutral words and non-smokers. This bias was associated with frontal relative positivity in the P300 time frame. Although these results are difficult to compare with those of Warren and McDonough (1999) because of different methodology (Word Stroop vs. passive picture viewing), both studies showed similar ERP activation patterns.

There are indications that processing biases are associated with subjective drug craving (see for a review Field et al., 2006; Franken, 2003). Recent research (Field et al., 2004) suggests that this relationship is bidirectional in nature: drug craving results in enhanced processing of drug-cues, but processing biases may result in enhanced craving. ERP measures of processing bias, i.e. enhanced P300 and SPW amplitudes have been found to correlate with drug craving, confirming this relationship. Namkoong et al. (2004) report subjective craving to be increased after drug-related picture presentation, and, moreover, this increase correlates significantly with P300 amplitude. Approximately the same is true for heroin abusers, who show a significant correlation between self-reported craving and SPW amplitude (Franken et al., 2003). Furthermore, in a study in which cocaine abusers are classified as ‘low cravers’ or ‘high cravers’, the latter show a more pronounced SPW in response to cocaine cues relative to neutral cues (Franken et

al., 2004). However, it must be noted that not all ERP studies of addiction find correlations between processing bias and craving (Van de Laar et al., 2004).

The relation between processing bias and craving has also been demonstrated in smokers (Mogg et al., 2003; Waters et al., 2003). Nevertheless, processing bias as measured by ERP failed to correlate with urge to smoke (Warren and McDonough, 1999). Clearly, more research is needed in order to resolve these issues.

Studies addressing the time-course of attentional biases in ex-smokers are scarce. A recent study using a dot-probe measure of attentional bias reveals that ex-smokers have an intermediate bias for smoking-related stimuli, falling in between smokers and nonsmokers (Ehrman et al., 2002). A second study using the modified Stroop paradigm reveals that there is actually no significant difference in attentional bias between never-smokers and ex-smokers (Munafo et al., 2003), indicating that processing biases do not appear to be a permanent feature of nicotine addiction. These results, in particular the latter, are in contrast with one specific notion of the incentive-sensitization model (Robinson and Berridge, 1993), predicting that the neuroadaptations are more or less permanently present, suggesting that drug-related cues retain their incentive-motivational properties after cessation of drug use. And therefore, processing biases will persist after cessation of smoking. Apparently, the issue whether attentional bias is a more or less permanent feature of nicotine addiction remains to be resolved. The present study addresses the question whether a smoking-associated processing bias is still present in ex-smokers after prolonged abstinence.

In order to investigate the permanency of smoking-related processing bias in ex-smokers, we conducted an ERP study in which we compared ex-smokers' later ERP

components in response to smoking-related and neutral pictures with those of smokers and never-smokers. Following the results of the aforementioned studies, one of the main hypotheses of the present study is that ex-smokers have less processing bias for smoking-related cues than smokers and that this bias approximates to never-smokers' bias, i.e. smoking-related cues are less motivational relevant for ex-smokers than for smokers and equally insignificant for ex-smokers as for never-smokers. Therefore it is hypothesized that ex-smokers, in response to smoking-related pictures, show less enhanced P300 and SPW amplitudes than smokers, whereas the P300 and SPW amplitudes of ex-smokers and never-smokers have approximately the same magnitude.

Since there is some evidence that attentional bias is associated with craving levels (Field et al., 2006; Franken, 2003), we also assessed smokers' and ex-smokers' subjective craving scores. It is expected that in the present study ex-smokers will report less subjective craving than smokers. Furthermore, the present study investigated the differences between smokers, ex-smokers and never-smokers in arousal and valence judgments of the smoking-related and neutral pictures. Previous studies show that smokers evaluate smoking-related pictures more positively than neutral stimuli (Geier et al., 2000; Hogarth and Duka, 2006, Mogg et al., 2003), whereas never-smokers evaluate them more negatively than neutral stimuli (Mogg et al., 2003). It is unknown how ex-smokers will judge the stimuli and if their scores will differ from those of smokers or never-smokers. Finally, both subjective craving and arousal and valence judgments are correlated with ERP amplitude. Because positive correlations are found in prior studies with drug-dependent individuals (Franken et al., 2004; Franken et al., 2003; Namkoong et al., 2004), they are predicted to be positively associated.

In addition, because Warren and McDonough (1999) not only found significant differences between smokers and never-smokers at the P300 component, but also at the N268 component (similar to the N300), differences between smokers, ex-smokers an never-smokers at this latter component were exploratively investigated in the present study.

Method

Subjects

Twenty-two smokers, 21 ex-smokers and 24 never-smokers were initially recruited by an advertisement placed at the psychology department of the Erasmus University Rotterdam (The Netherlands). All participants were screened by telephone for study eligibility (smoker status, and cigarettes/day). Smokers were eligible if they smoked ten cigarettes or more per day. Ex-smokers were participants who quit smoking at least six months ago and did not smoke a single cigarette within that period. Never-smokers were included if they had not smoked more than three cigarettes in their lifetime.

Seven participants (1 smoker; 3 ex-smokers; 3 never-smokers) were excluded from the analyses because of excessive artifacts in the EEG-signal (>50% of the epochs), resulting in a final group of 21 smokers (mean age 21.6 years, SD= 2.5 years), 18 ex-smokers (mean age 23.1 years, SD= 4.1 years) and 21 never-smokers (mean age 19.6 years, SD= 1.2 years). The age difference between the groups was significant ($F_{2,59}$= 8.1, $p< 0.01$). Never-smokers were younger than smokers and ex-smokers. However, no correlations were found between age and the ERP measures (N300, P300 and SPW),

indicating that age is not a confounding variable[1]. Smokers and ex-smokers did not differ in smoking duration (smokers= 4.8 years, SD= 2.8 years; ex-smokers= 5.3 years, SD= 3.0 years; t((37)= 0.56, p= 0.58) nor in nicotine dependence (smokers' Fagerström Test of Nicotine Dependence (FTND) score= 3.6, SD= 2.2; ex-smokers' FTND score= 2.7, SD= 2.4; t(37)= 1.30, p= 0.20). Smokers smoked between 10 to 30 cigarettes a day (13.6%: approximately 10 cigarettes, 81.8%: 11-10 cigarettes, 4.5%: 21-30 cigarettes). Ex-smokers smoked also 10 to 30 cigarettes a day (42.9%: approximately 10 cigarettes, 38.1%: 11-20 cigarettes, 19.0%: 21-30 cigarettes). The mean quit duration of ex-smokers was 1.4 years (SD=1.8). The groups consisted predominantly of undergraduate psychology students, who received course credit or a small financial compensation for participation. The study was approved by the institutional ethical board.

Experimental stimuli

Stimuli consisted of 16 different smoking-related pictures and 16 nonsmoking-related, neutral pictures. The smoking-related stimuli consisted of ten digital photographs of persons holding, lighting up, or smoking a cigarette and six photographs of attributes related to smoking activity, such as packs of cigarettes and a burning cigarette in an ashtray. These scenes with smoking-related cues represented situations are known to produce smoking cue-reactivity in smokers (Niaura et al., 1992) and are associated with smoking relapse in ex-smokers (Baer and Lichtenstein, 1988). The neutral stimuli consisted of photographs identical to the smoking-related photographs (i.e. the same persons, same location, same pose), only without visible smoking activity, and displaying

[1] In addition, age was added as covariate in all analyses. No significant main nor interaction effect of age was found. Therefore, we report the analyses without age as covariate.

neutral objects (e.g. a spoon) that were unrelated to smoking behavior. This way, it was controlled for contrast, brightness and other possible confounding factors. All pictures were presented full-screen on a 15" color monitor located at approximately eye level about 1 m in front of the participants.

Procedure

Smokers were asked to abstain from smoking for at least one hour before the experiment. This short period of smoking deprivation served to reduce possible acute nicotine effects on ERP amplitude, which are found in several studies (Houlihan et al., 1996; Houlihan et al., 2002). Participants were tested alone in a light and sound-attenuated room. After obtaining informed consent, participants completed a questionnaire about demographics and smoking history. After completion, participants were seated in the EEG chair and electrodes were attached. Instructions were to sit relaxed and still, and to carefully attend to all pictures without employing distracting thoughts. Then the task was started.

Each of the 16 smoking-related and 16 neutral stimuli were repeated four times resulting in a total of 128 stimulus presentations. Stimulus presentations from the two categories were varied in a quasi-random fashion to prevent order and 'oddball' effects. There were no successions of more than four stimuli from the same category. Stimuli were presented for 2000 ms, with an inter-stimulus interval randomly varying from 1800 to 2200 ms (with an average of 2000 ms).

After the picture viewing, electrodes were removed and smokers and ex-smokers filled-out the brief Questionnaire on Smoking Urges (QSU-brief; Cox et al., 2001). In

addition, all participants rated the pictures on their arousal and valence properties. After having completed the experiment, subjects received their course credit or financial compensation.

Self-report measures

Demographic and smoking history data were self-reported (age, smoking duration, and period(s) of abstinence). Subjective craving was measured by the 10-item QSU-brief (Cox et al., 2001). This 10-item questionnaire was adapted from the Questionnaire on Smoking Urges (QSU; Tiffany and Drobes, 1991) and consists of two subscales: "desire and intention to smoke", and "reduction of negative affect and withdrawal symptoms". These subscales have adequate psychometric properties (Cox et al., 2001).

Strength of smoking habit was assessed by means of the Dutch version of the Fagerström Test for Nicotine Dependence (FTND; Vink et al., 2005). This questionnaire has good reliability and correlates significantly with number of cigarettes smoked per day. The FTND consists of six items, which are scored according to the scoring system described in Heatherton et al. (1991). Ex-smokers filled-out the FTND retrospectively. Retrospectively assessed FTND scores have adequate psychometric properties (Hudmon et al., 2005).

Valence and arousal properties of the pictures were assessed by 10 cm Visual Analog Scales (VAS). The valance scale ranged from very pleasant (0 cm) to very unpleasant (10 cm); the arousal scale ranged from doesn't arouse me (0 cm) to arouses me much (10 cm). For this task, the pictures were printed in color ink on white paper.

Physiological measures

EEG was measured with a digital BioSemi amplifier using Ag/AgCl electrodes at 34 scalp sites according to the International 10/20 system (32 standard channels including left and right mastoid locations). The vertical electro-oculogram (VEOG) was recorded with two Ag/AgCl electrodes located above and underneath the left eye. The horizontal electro-oculogram (HEOG) was recorded with two Ag/AgCl electrodes located at the outer canthus of each eye. All signals were digitized on a PC with a sample rate of 256 Hz and 24-bit A/D conversion. Off-line, EEG and EOG were filtered using a 0,1-30 Hz (24 dB/Oct roll off) band-pass filter. Four scalp electrodes (Fz, Cz, Pz, Oz) were used in the present study.

Data reduction and analysis

EEG and EOG recordings were segmented in 950 ms epochs, including 100 ms pre-stimulus baseline. Gratton and Coles algorithm (Gratton et al., 1983) was used for correction of vertical and horizontal eye movements, and eye blinks. After ocular correction all segments with an EEG activity above -/+ 100 μV were excluded from further analysis. A 100 ms pre-stimulus baseline correction was applied, and epochs were averaged across trials. Overall grand averages were obtained for each picture category in the three groups. The resulting ERP-waves were visually inspected and appeared to correspond well with ERP-waves usually reported in response to visual stimuli (see Figure 1 for a representation of the separate waves at electrode Fz). Three ERP components were investigated: a negative waveform captured by a 220-300 ms time

window (most similar to the traditional N300), a positive waveform from 300 to 400 ms (traditional P300) and a slow positive wave captured by a 500-750 ms time window (SPW). Mean maximum amplitudes were computed per group and stimulus category for the aforementioned time windows. Since no clear peaks were observed in the 500-750 ms time range, area measurement (mean activity) was applied here.

Statistical analysis

For each time interval, ERP effects were assessed by performing repeated-measurement analyses of variance (ANOVA) on the four midline electrode sites (Oz, Pz, Cz, and Fz). Group (smokers, ex-smokers, and never-smokers) served as the between-subjects factor, and cue type (neutral versus smoking-related) and midline site (Oz, Pz, Cz and Fz) served as within-subjects factors. This resulted in a 4 (midline site) x 2 (cue) x 3 (group) repeated measures ANOVA. To assess relationships between cue-evoked ERP amplitudes, craving levels, and valance/ arousal assessments, Spearman correlation coefficients were calculated between significant ERP amplitudes, self-reported craving levels, and valence/ arousal judgments. Arousal and valance ratings of the pictures were tested using two 2 (cue type) x 3 (group) repeated-measurement ANOVA's. To examine exact differences between groups and cues, pairwise post-hoc follow-up analyses with Bonferroni correction were applied to all ANOVAs. Greenhouse-Geisser correction was applied to all ANOVAs when necessary. An alpha-level of 0.05 was used for all statistical tests.

Results

Because our interest concerned mainly group differences, only Group and Group interaction effects are reported. In order to reduce the number of ERP results, and in line with the hypotheses of the study, we report only significant (or border-significant) Group or Group-interaction effects. The averaged ERP waveforms on the neutral and smoking-related stimuli for smokers, ex-smokers, and never-smokers are displayed in figures 2-4. In tables 1-3, the mean and standard deviations of the ERP components are displayed.

N300

For the N300 peak, no significant main effect of Group (G), Group (G) x Cue (C) interaction nor G x C x Site (S) interaction effects could be observed ($F < 0.55$, NS) on any of the midline sites.

P300

For the P300 peak, a G x C interaction effect was found, $F_{3,171}= 3.83$, $p<0.05$. Post-hoc comparisons revealed no significant differences between smokers, ex-smokers and never-smokers on neutral cues. On the smoking-related cues P300 amplitude was significantly larger for smokers than for never-smokers ($p< 0.005$) or ex-smokers ($p< 0.05$), whilst no significant differences were found between ex-smokers and never-smokers ($p= 1$). Besides a significant G x C interaction, a G x C x S interaction effect was found, $F_{3,171}= 3.46$, $p< 0.01$. Post-hoc analyses showed that at none of the single electrodes (Fz, Cz, Pz, and Oz) groups differed in their P300 response to nonsmoking-related, neutral pictures. However, in response to smoking-related pictures several differences were found. At Fz,

P300 amplitude was more enhanced for smokers than for never-smokers ($p< 0.05$) and ex-smokers ($p< 0.05$). At this site never-smokers' P300 amplitude did not differ from ex-smokers' P300 amplitude ($p= 1$). Almost the same differences were found at Cz: Smokers showed a more enhanced P300 amplitude than never-smokers ($p< 0.005$), ex-smokers showed a less enhanced P300 amplitude than smokers ($p< 0.05$), but ex-smokers' P300 amplitude did not differ from the never-smokers' amplitude ($p= 1$). At Pz, P300 amplitude differed between smokers and never-smokers ($p< 0.005$). No effects were found at Oz.

SPW

No significant G x C interaction was found for the SPW, $F_{3,171}= 2.39$, $p= 0.10$. However, a G x C x S interaction effect was revealed, $F_{3,171}= 2.39$, $p< 0.05$. Follow-up comparisons showed that the three groups did not differ in SPW response to neutral pictures on any of the sites. These comparisons also revealed that in response to smoking-related pictures smokers' SPW amplitude at Fz was significantly more enhanced than never-smokers' SPW amplitude ($p< 0.05$) an ex-smokers' SPW amplitude ($p< 0.05$). However, ex-smokers' and never-smokers' SPW amplitudes did not differ at Fz ($p= 1$). At Cz, smokers displayed a significantly larger SPW amplitude than never-smokers ($p< 0.05$). The difference between smokers and ex-smokers nearly reached significance ($p= 0.061$), whereas no difference between ex-smokers and never-smokers was found ($p= 1$). At Pz and Oz electrodes no significant SPW amplitude differences were found between groups.

Self-reported craving and ERP waves

The scores on the post-exposure QSU-brief were significantly higher for smokers (M= 39.4, SD= 9.0) than for ex-smokers (M= 19.11, SD= 9.6), $t(37)= 6.83$, $p< 0.01$. This difference is mainly the result of a difference between the groups in scores on the first subscale 'desire and intention to smoke', $t(37) = 10.03$, $p< 0.01$. Smokers did not differ from ex-smokers on the second subscale 'reduction of negative affect and withdrawal symptoms', $t(37)= 1.84$, NS.

No significant correlations were observed between SPW amplitude differences (response to smoking-related cues minus response to neutral cues) on the four midline sites on the one hand and self-reported craving on the other. However, at the P300 peak, Fz amplitude difference correlated significantly with the first subscale of the QSU-brief, "desire and intention to smoke", $r = 0.32$, $p< 0.05$. Therefore the greater the desire and intention to smoke, the larger the Fz amplitude in response to smoking-related pictures relative to Fz amplitude in response to neutral pictures.

Valence and arousal properties of smoking-related pictures and ERP waves

Concerning arousal and valence ratings, we were interested in Cue (C) x Group (G) effects. Therefore, we only report these interaction effects. See table 4 for the mean ratings. On the arousal ratings we found a significant C x G interaction effect, $F_{2,57}= 7.47$, $p< 0.05$. Post hoc tests showed that there were no group effects for the neutral cues (all p's NS). However, a group effect for the smoking-related cues was found. The arousal score of smoking-related pictures was significantly greater for smokers than for never-smokers ($p< 0.05$), but did not differ between smokers and ex-smokers ($p= 0.90$) and ex-

smokers and never-smokers ($p= 0.240$), which implicates that the arousal ex-smokers experienced falls in between the arousal smokers and never-smokers experience in response to smoking-related pictures. Within-group differences in self-reported arousal were observed between neutral and smoking-stimuli among smokers ($p< 0.001$) and ex-smokers ($p<0.001$), but not in never-smokers ($p = 0.08$). Both smokers and ex-smokers reported more arousal on smoking pictures than on neutral pictures.

Concerning valence ratings, we also found a significant C x G interaction effect $F_{2,57}= 18.17$, $p< 0.001$. Post-hoc tests showed that there were no group effects for the neutral cues (all p's NS). However, the valence score of smoking related pictures was greater for smokers than never-smokers ($p< 0.001$), greater for smokers than ex-smokers ($p< 0.001$) and did not differ between never-smokers and ex-smokers ($p= 1$). This implicates that ex-smokers and never-smokers found smoking-related pictures less pleasurable than smokers and that ex-smokers found these pictures as unpleasant as never-smokers. Within-group differences in self-reported valence were observed between neutral and smoking-stimuli were found and ex-smokers ($p<0.05$), and never-smokers ($p< 0.05$). Never-smokers and ex-smokers evaluated smoking-related pictures as less pleasurable than neutral pictures. Self-reported valence differences were also observed between neutral and smoking-stimuli in smokers ($p< 0.05$). In contrast to ex-smokers and never-smokers, smokers rated smoking-related pictures significantly more pleasurable than neutral pictures.

Correlations between SPW amplitude differences on midline sites and both arousal and valence difference scores (evaluation of smoking-related pictures minus neutral pictures) were not significant. In addition, no significant correlations were found

between P300 amplitude difference and valence difference score. For this component, however, a significant correlation emerged between Fz amplitude difference and valence difference score ($r = -0.29$, $p < 0.05$) and between Cz amplitude difference and valence difference score ($r = -0.26$, $p < 0.05$), suggesting that the greater the frontal and central amplitude difference in response to smoking-related pictures and neutral pictures, the lower the valence score given to the smoking-related pictures relative to neutral pictures, that is, the more pleasurable the smoking-related pictures are found.

Discussion

The present study investigated processing bias of smoking-related stimuli in smokers, ex-smokers and never-smokers employing ERP measurements. Several hypotheses were formulated concerning group differences in smoking-related and neutral cue-evoked ERP waves. The main hypothesis was that smoking-related pictures have greater motivational salience and therefore smokers would display enhanced processing of these pictures compared to ex-smokers and never-smokers. Since enhancement of amplitudes of later ERP components is believed to reflect increased processing, it was hypothesized, more specifically, that smokers would show more enhanced amplitudes of the later ERP components in response to smoking-related pictures than ex-smokers and never-smokers. This hypothesis is confirmed by the results of the present study. Both the P300 and SPW amplitudes in response to smoking-related pictures are significantly more enhanced for smokers than for ex-smokers and never-smokers at frontal and central sites, whereas the magnitude of the P300 and SPW amplitudes in response to neutral pictures does not differ between the three groups. Accordingly, it can be concluded that smokers show

more bias for smoking-related pictures than ex-smokers and smokers. Because there is no significant difference between the P300 and SPW amplitudes of ex-smokers and never-smokers, it can also be concluded that ex-smokers display the same amount of processing bias as never-smokers.

From previous studies using electrophysiological measures of emotional information processing it has become apparent that motivational relevant stimuli, such as emotional pictures attract attention (Cuthbert et al., 2000; Lang et al., 1997; Lang et al., 1998; Schupp et al., 2003; Vuilleumier, 2005). It has been suggested that increased slow waves of the ERP reflect an increased allocation of attentional resources to motivational relevant (emotional) stimuli, also described as "motivated attention" (Lang et al., 1997; Schupp et al., 2004). In this context, the present findings on the processing of smoking stimuli are in line with studies using more specific attentional bias measures of smoking-related processing, such as the smoking Stroop task.

Our findings are fully in line with the results of Munafo et al. (2003), who found a significant difference in attentional bias between smokers and ex-smokers but no difference between ex-smokers and never-smokers. Although the findings are generally in line with an incentive sensitization view of addiction (Robinson and Berridge, 1993), the present findings also contradict the prediction of Robinson and Berridge that the neural adaptations, which result in an enhanced processing of drug cues in former drug users, are a permanent feature of addiction. The current findings suggest that in ex-smokers, at least to some extent, extinction of the cortical reactivity towards smoking cues has taken place. The P300 and SPW differences between smokers and ex-smokers and the absence of these differences between ex-smokers and never-smokers in the

present study show that the property of smoking related cues to enhance cortical processing is not a permanent feature and, at least partly, reversible.

The P300 discrepancies between smokers and never-smokers found in the present study are to a large extent in accordance with the results reported by Warren and McDonough (1999). The smokers in their study showed larger positive P412 (comparable to the P300 component in our study) differences at Cz and Fz to the two types of stimuli (smoking-related minus neutral stimuli) compared to never-smokers. The P300 differences between smokers and never-smokers in the present study are comparable, in that they are also found at Fz and Cz. In contrast to our study, Warren and McDonough (1999) did not find any differences between smokers and never-smokers on the SPW component. The finding that there are SPW differences between smokers, never-smokers and ex-smokers in the present study is in line with results from previous studies among heroin abusers (Franken, 2003) and cocaine abusers (Franken et al., 2004; Van de Laar et al., 2004). A possible explanation for the presence of SPW differences in the present study but their absence in the study of Warren and McDonough (1999), is the utilization of different stimulus material. Present material appears to be more attractive than the material used by Warren and McDonough. The smokers in their study did not evaluate the smoking-related stimuli significantly more pleasurable than neutral stimuli, whilst the smokers in the present study do. Besides, the stimuli presented in the present research were shown for a longer time compared to Warren and McDonough (2000 versus 150 ms), allowing more elaborative processing of the stimuli, which results in a larger SPW component.

It should be noted, however, that the distinction between the P300 and the SPW component is rather arbitrary. It is possible that these two components in fact represent only one component, i.e. one information processing operation. The positive wave from 400 to 750 ms, labeled SPW in the present study, could be part of or an extension of the P300.

In the present study no significant N300 differences were found between smokers, ex-smokers and never-smokers. This is in contrast with Warren and McDonough (1999) who found a difference between smokers and never-smokers on the N268 component, that is the amplitude of this N300-like component was significantly more enhanced in response to neutral cues than in response to smoking-related cues. The authors suggested that this component probably depicts the neutral pictures' lack of fit to the smokers' functional or subjective tobacco-addicted states. A possible explanation for this inconsistency on the N300 between the present study and that of Warren and McDonough (1999) is that the smokers in the present study had more difficulty detecting differences between smoking-related and neutral pictures because they were practically identical except for the presence or absence of smoking activity. However, future investigation of the N300 component in addiction is necessary.

Another objective of the present study was to examine the relationship between processing bias and drug craving. After picture viewing smokers report significantly more craving than ex-smokers, which is congruent with smokers exhibiting greater amplitude differences than ex-smokers. Furthermore, the craving subscale 'desire and intention to smoke' appears to be significantly and positively correlated with frontal P300 amplitude. The robustness of this finding is confirmed by the correlation between the

frontal P300 amplitude and the valence judgment. These findings implicate that the more pleasant the smoking-related pictures are found and the more desire and intention to smoke they induce, the greater the frontal P300 amplitude difference between smoking-related and neutral pictures, i.e. the more enhanced the attentive processing of smoking-related cues.

The correlation with only one aspect of craving (i.e., 'desire and intention to smoke' but not 'reduction of negative affect') is consistent with a positive-incentive view of addiction (Robinson and Berridge, 1993; Stewart et al., 1984), which predicts that not the negative withdrawal symptoms, but mainly the positive-incentive features of drug stimuli elicit craving.

It should be noted that only the frontal P300 amplitude correlates with self-reported craving, and that this relation is moderate. The absence of a stronger correlation, observed in other studies addressing the relation between drug craving and processing bias (Franken et al., 2004; Franken et al., 2003; Namkoong et al., 2004), may be attributable to the fact that smoking cravings are less explicit than cocaine, heroin, and alcohol craving.

A limitation of the present study is that we did not measure the perceived availability to smoke cigarettes. Although all groups had technically the same opportunity to smoke after the experiment, it might be that the perceived availability of ex-smokers was reduced because of their higher motivation to keep abstinent. It is known that perceived availability is associated with craving levels (Wertz and Sayette, 2001) and other drug-related responses (Hogarth and Duka, 2006; Wilson et al., 2004). The influence of perceived availability on ERP measures of processing has not been

addressed before. Another limitation is that our smokers and ex-smokers samples mainly consisted of relatively light-smokers. Only a small minority of the (ex-)smokers smoked more than 20 cigarettes a day. It awaits further study whether the present findings can be generalized to heavy (ex-)smokers. Another point that should be addressed in future research is how long after smoking cessation the processing biases to smoking cues persist. In the present study we found no evidence for a processing bias in ex-smokers who were abstinent for at least 6 months. Inclusion of a recently abstinent group would yield more insight in the time course of the extinction of processing biases.

The main conclusion of the present study is that smokers and ex-smokers process smoking-related pictures differently, whereas ex-smokers and nonsmoker appear to process smoking-related pictures more or less in the same way. The slow components of the ERP are more enhanced for smokers than for ex-smokers in response to smoking-related pictures, whereas there are no significant ERP differences between ex-smokers and never-smokers. This indicates that ex-smokers show less processing bias for smoking-related cues than smokers and above all that this bias diminishes to the bias level of never-smokers. Therefore, it appears that processing bias is not a permanent feature of nicotine addiction. Furthermore, we found a relation between amplitudes of the P300 component and self-reported craving.

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Acknowledgements

We would like to thank Ivo van de Berg for assisting with the data-collection

Table 1: Mean amplitudes (in μV) of N300, P300 and slow positive wave (SPW) on smoking-related and neutral cues at midline sites (Fz, Cz, Pz, and Oz) for ex-smokers.

Component	Site	$M_{smoking\text{-}related}$ (SD)	$M_{neutral}$ (SD)
N300	Fz	-9.39 (6.00)	-9.99 (6.39)
	Cz	-6.38 (7.32)	-6.72 (7.03)
	Pz	2.09 (7.39)	1.86 (7.55)
	Oz	7.08 (2.59)	7.56 (2.84)
P300	Fz	-0.28 (6.21)	-2.45 (5.48)
	Cz	4.33 (7.35)	1.25 (6.13)
	Pz	12.02 (7.27)	9.20 (5.96)
	Oz	11.42 (3.42)	10.40 (3.37)
SPW	Fz	0.63 (6.11)	-1.53 (4.75)
	Cz	5.29 (6.47)	2.90 (4.60)
	Pz	8.73 (5.05)	6.84 (3.54)
	Oz	6.31 (3.10)	5.88 (3.21)

Table 2: Mean amplitudes (in μV) of N300, P300 and slow positive wave (SPW) on smoking-related and neutral cues at midline sites (Fz, Cz, Pz, and Oz) for smokers.

Component	Site	$M_{smoking\text{-}related}$ (SD)	$M_{neutral}$ (SD)
N300	Fz	-6.84 (4.89)	-8.77 (5.42)
	Cz	-2.29 (5.45)	-4.23 (6.35)
	Pz	5.01 (6.98)	4.36 (7.86)
	Oz	8.26 (5.92)	8.84 (5.50)
P300	Fz	5.21 (6.88)	0.56 (6.45)
	Cz	10.13 (6.26)	5.74 (6.86)
	Pz	15.91 (6.63)	12.70 (7.20)
	Oz	11.83 (5.87)	11.05 (5.40)
SPW	Fz	5.28 (5.51)	1.06 (5.29)
	Cz	9.44 (5.69)	5.67 (5.39)
	Pz	9.69 (6.35)	7.37 (6.04)
	Oz	5.43 (5.69)	4.94 (4.96)

Table 3

Mean amplitudes (in μV) of N300, P300 and slow positive wave (SPW) on smoking-related and neutral cues at midline sites (Fz, Cz, Pz, and Oz) for never-smokers.

Component	Site	$M_{smoking\text{-}related}$ (SD)	$M_{neutral}$ (SD)
N300	Fz	-6.18 (5.19)	-7.18 (4.45)
	Cz	-3.53 (4.97)	-4.78 (4.33)
	Pz	0.76 (4.70)	0.33 (4.75)
	Oz	4.78 (4.80)	4.95 (5.42)
P300	Fz	0.52 (4.64)	-0.94 (4.02)
	Cz	3.17 (4.80)	2.40 (4.30)
	Pz	8.88 (6.37)	8.05 (6.42)
	Oz	9.49 (5.90)	9.31 (5.84)
SPW	Fz	0.97 (3.58)	0.49 (3.82)
	Cz	4.74 (3.92)	3.64 (3.50)
	Pz	6.19 (4.51)	6.05 (4.37)
	Oz	4.05 (4.33)	4.65 (3.61)

Table 4. Mean self-reported arousal and valence ratings (SD) of the three samples.

		Never-smokers	Smokers	Ex-smokers
Arousal	Neutral	2.7 (1.4)	2.3 (1.7)	2.8 (1.8)
	Smoking	3.5 (2.5)	5.6 (2.0)	4.8 (2.2)
Valence	Neutral	4.9 (1.2)	4.8 (0.5)	4.6 (0.7)
	Smoking	6.3 (1.9)	4.2 (1.2)	6.3 (1.4)

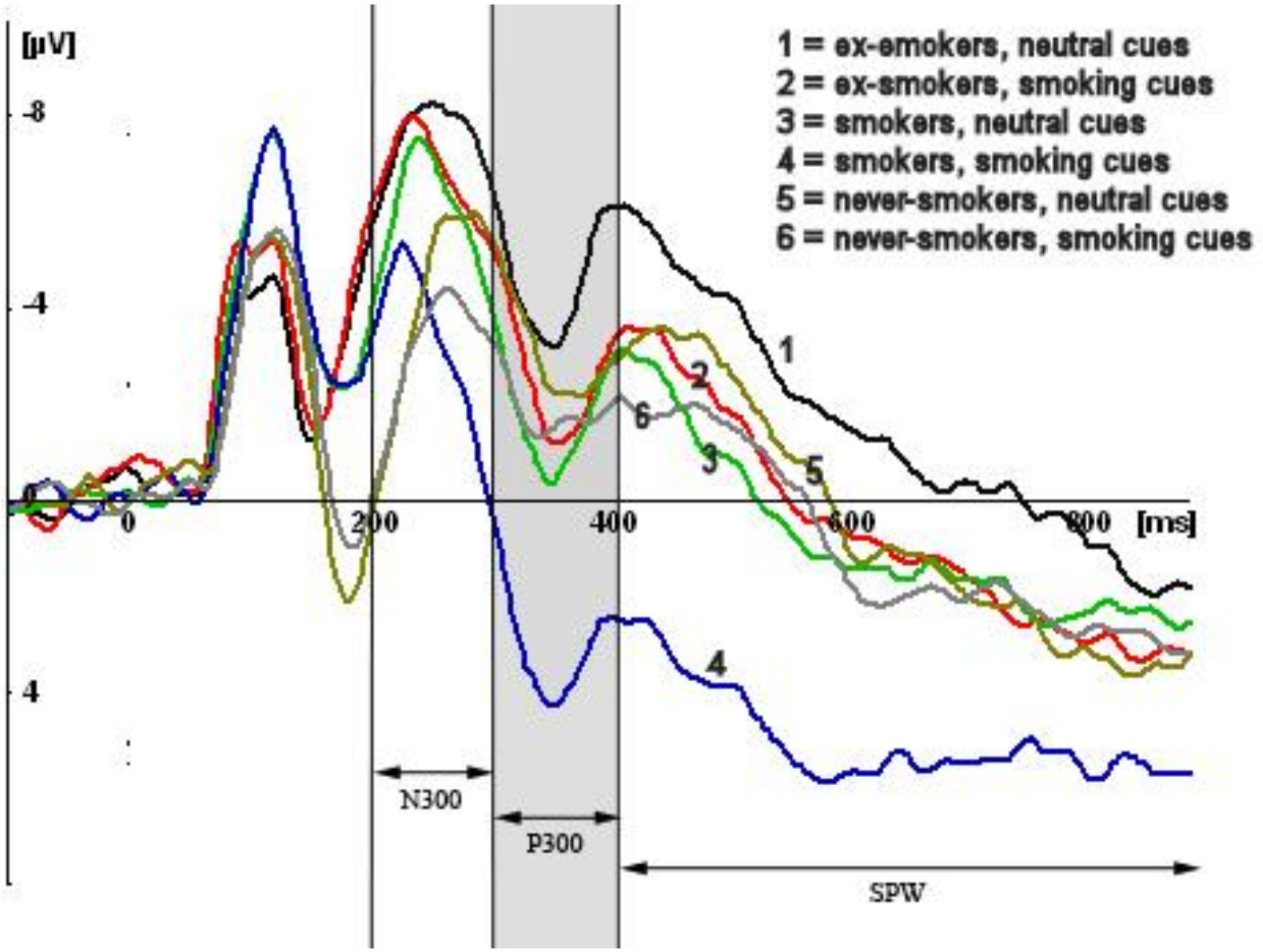
Figure captions

Figure 1. Specific time-frames of the N300, P300 and slow positive wave (SPW) components.

Figure 2. Average event-related potentials at the frontal (Fz) site for smokers in response to neutral pictures (black) and smoking-related pictures (red).

Figure 3. Average event related potentials at the frontal (Fz) site for ex-smokers in response to neutral pictures (black) and smoking-related pictures (red).

Figure 4. Average event related potentials at the frontal (Fz) site for never-smokers in response to neutral pictures (black) and smoking-related pictures (red).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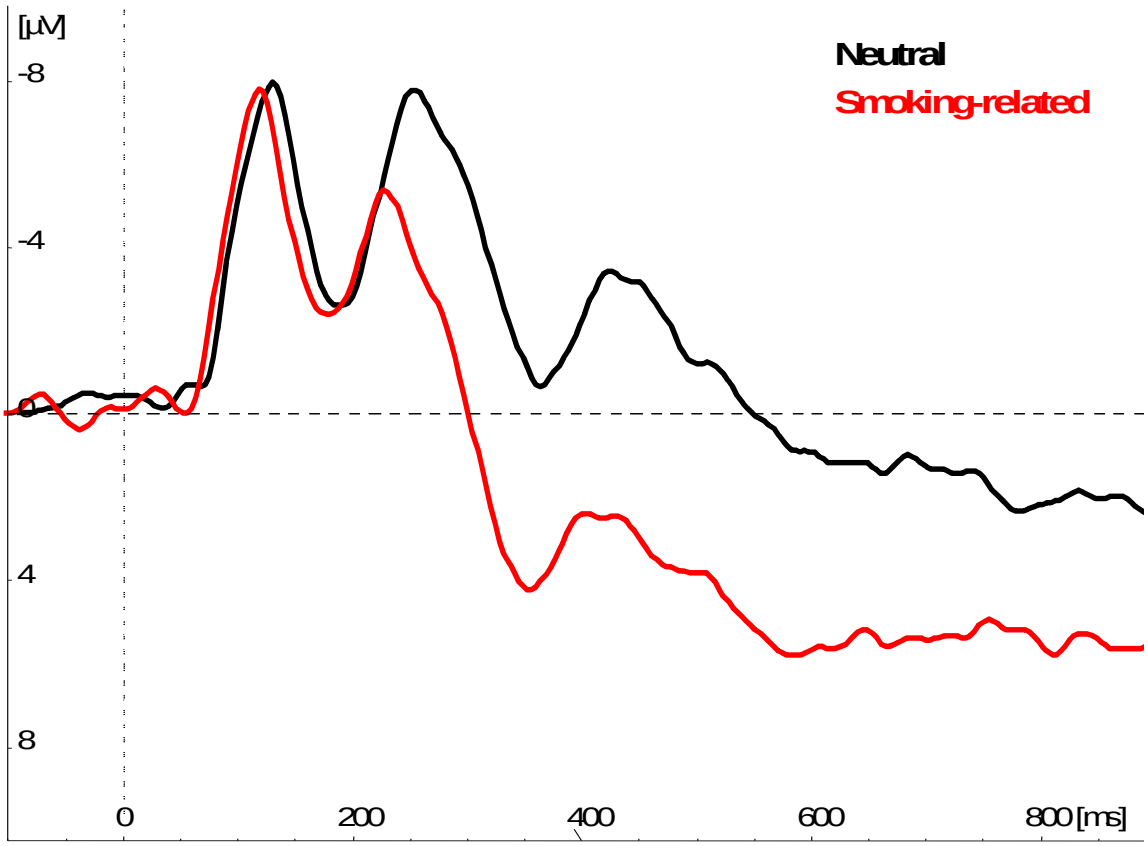
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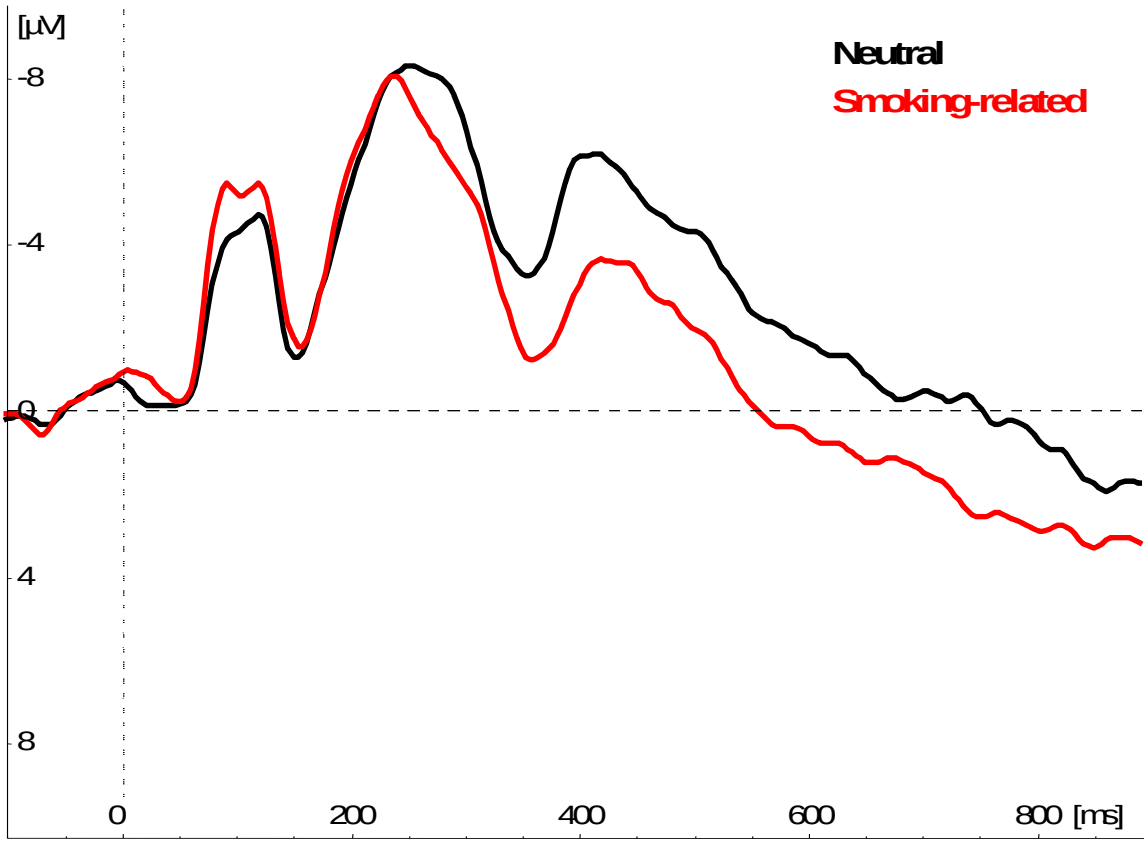
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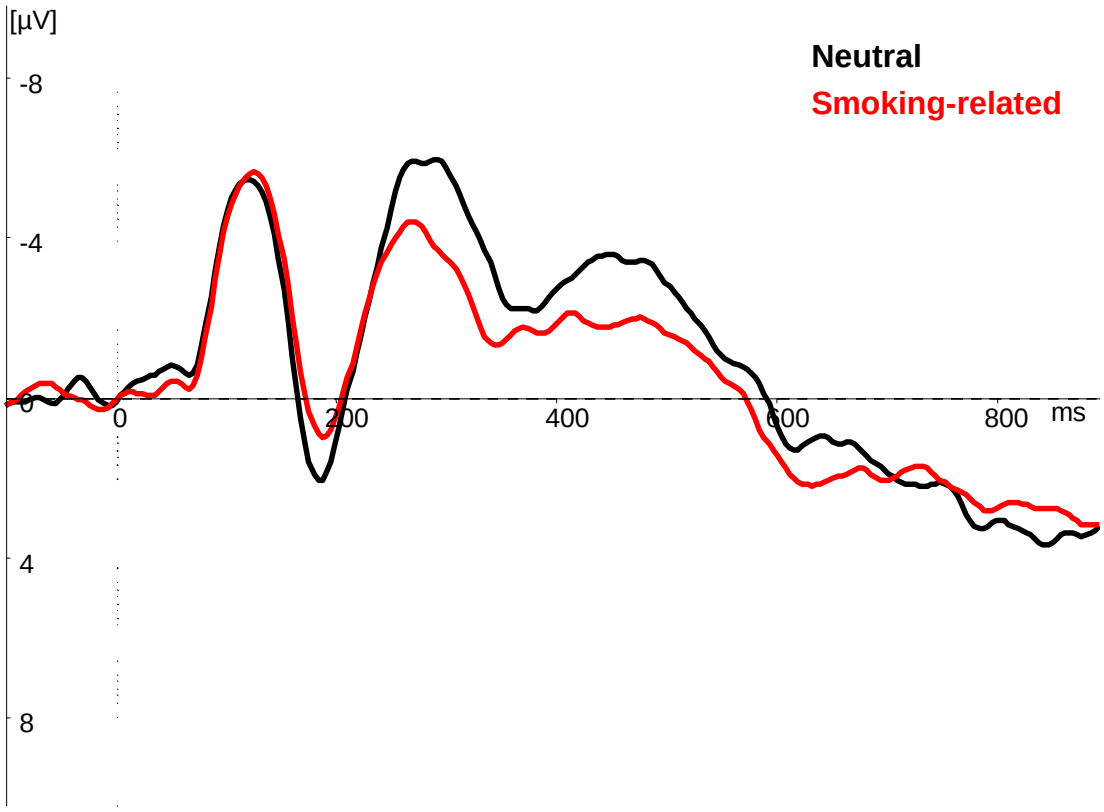
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