Differences in ERP topographies during color matching of smoking-related and neutral pictures in smokers and non-smokers

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Abstract

The concept of a specific memory network that drives addictive behavior has often been discussed in relation to the phenomenon of sudden relapse into addiction after years of abstinence. But there is still a lack of data that shows a link between drug-related cue processing and specific changes of behavior in addicts. In the present study we investigated the relationship between smoking-related picture processing, performance in a color matching task, and ERP topographies. Fifteen smokers and 19 non-smoking participants performed a color matching task including monochromic pictures with smoking-related and neutral content. Smokers and non-smokers showed remarkable differences between stimulus category-related ERP topographies. Furthermore, both smokers and non-smokers showed increased reaction times during color matching when the picture contents were related to smoking behavior. The results are discussed with respect to different drug-cue-related patterns of information processing in smokers and non-smokers.
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1. Introduction

1.1. Addiction memory

Based on animal studies, Wolffgramm and Heyne (1995) described four phases in the development of addiction during which a complex memory engram is elaborated. This engram labeled as addiction memory links several aspects such as emotional states, environmental factors, and substance-related features (e.g., taste, smell and consistence of the drug). The association between emotional states – modulated by the limbic brain system – and the strong behavioral and physiological reinforcement of drug-related cues might lead to an intense consolidation of memories comparable to those elaborated by imprinting processes. It is important to note, that the rats in Wolffgramm's studies needed to voluntarily consume the drug to develop an addiction memory, whereas forced consumption did not lead to the same effect. Thus, it has been discussed that aspects, such as voluntary emotional and/or mood states, related to consuming behavior may play a crucial role in the development of addiction (Boening, 1994, 2001). The hypothesis that there seems to be a strong consolidation, not only of aspects associated with direct drug consumption, but also of indirect smoking-related cues is supported by the fact that nicotine and smoking seems to take an effect especially on reticular (arousal related) activating systems and limbic (emotion, motivation, and memory related) systems with the hippocampus being most noticeably affected (for review see Conrin, 1980; see also Polich and Criado, 2006).

The above mentioned notions are supported by frameworks considering network models, following the basic tenet that cognitive representations consist of widely distributed and interacting networks of cortical neurons (e.g., Fuster, 2006; Basar,

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2005, 2006). Within this framework it is proposed that the association cortex of e.g., posterior-post-rolandic-regions contain perceptual units, i.e., networks made of neurons associated by information acquired through senses. The frontal association cortex, however, contains executive units, relying on neurons associated by information related to action. These posterior and frontal networks are connected by long reciprocal cortico-cortical connections, and these associations are suggested to support the dynamics of the perception–action cycle in behavior, speech and reasoning (Fuster, 2006; Basar, 2005, 2006). Thus, it is postulated that the constant reciprocal activations are based on an alliance including subprocesses of attention, perception, learning and remembering (Basar, 2004, 2005). It is suggested that all cognitive brain functions are inseparable, e.g., from memory and perceptual functions, and that the units and their interplay can be observed as responsiveness of the brain, and measured as modulations in EEG and ERP parameters (Basar, 2005, 2006; Basar et al., 2000).

A central question arising from the described results and frameworks is the following: are there changes in specific perception–action cycles due to altered networks and/or increased consolidation during development of addictive behavior? Can indicators for these changes be observed on behavioral and/or neurophysiological levels?

1.2. Nicotine consumption and ERPs

At physiological level, persisting nicotine effects on brain activity, such as ERPs and oscillatory brain responses, have been shown in animal and human studies (for review see Polich and Criado, 2006; Ilan and Polich, 2001; Polich and Ochoa, 2004; Haarer and Polich, 2000; Slawecki et al., 2000; Slawecki and Ehlers, 2002, 1998; Roos, 1977; Domino, 2003; Anokhin et al., 2000). Nicotine administration also directly influences brain oscillations in different brain regions (Crawford et al., 2002; Braus et al., 2003; Kumari et al., 2003; Pritchard et al., 1995) and increases cognitive performance in smokers and in non-smokers (Kumari et al., 2003; Lawrence et al., 2002; Pritchard et al., 1995; Lindgren et al., 1998, Cohen et al., 1994; Le Houezec et al., 1994; and others).

The most consistent findings have been reported for the P300, usually using target discrimination tasks. A large scale study by Anokhin et al. (2000) and a study by Polich and Ochoa (2004) including low-, high-rate, former and never-smokers suggests that P300 amplitudes to target detection, but not to standard stimuli processing, were smaller in all subjects who had smoked, with highest reductions in current smokers. In addition, acute nicotine intake, compared to placebo treatment, has been reported to especially lead to increased fronto-central P3a amplitudes in smokers (Polich and Criado, 2006). A review of studies using different kinds of subject groups, tasks and task difficulties, however, indicates that it is important not only to take aspects such as drug deprivation, acute or chronic intake, smoking history and poly drug abuse into account, but that increased task difficulty and task type may also influence ERP differences between smokers and non-smokers (e.g., Polich and Ochoa, 2004; Polich and Criado, 2006).

1.3. Physiological influence of nicotine consumption and addiction-related cues

Smokers are especially at risk for relapse because nicotine consumption can transiently "normalize" or enhance their arousal as well as their cognitive performance to levels shown before chronic nicotine consumption (Kumari et al., 2003; Lawrence et al., 2002; Pritchard et al., 1995; and others). Improvement and/or normalization of cognitive performance levels by smoking and/or alternative nicotine administration is suggested to be a strong reinforcer increasing sensitivity for all environmental and behavioral drug-related situations during the development of addiction. Aspects of these situations might be embedded in a complex drug-related engram (i.e., addiction memory) responsible for motivated behavior and consolidated as networks sensitive to cues inducing drug seeking and consumption behavior.

Numerous studies have shown that behavioral and/or environmental cueing, using specific aspects of drug consumption, can produce changes in the feeling of craving and physiological parameters, such as skin conductance, heart rate and EEG-related parameters (Carter and Tiffany, 1999). Consuming de-nicotinized cigarettes and even sham smoking has been shown to reduce craving and change vegetative as well as brain activity (Pickworth et al., 1999, 2003; Baldinger et al., 1995; Domino and Matsuoka, 1994; Hori et al., 1994; Cohen et al., 1994; Kumar et al., 1977; Teter et al., 2002; Hasenfratz et al., 1993).

In an ERP study, Franken (2003) reported that cocaine as well as heroin addicts showed an augmented late slow positive wave and feelings of craving during presentation of substance-related pictures. Complementarily, Warren and McDonough (1999) found that moderate smokers showed relative lower N268 and higher P412 during the confrontation with smoking-related motives at collapsed mid-frontal, -central and parietal electrode sites. Similarly, using addiction-cue-word-information within a word–color-matching task, differences in ERP topographies between smokers and non-smokers were found in early (around 100 ms after stimulus onset) and late time windows (Fehr et al., 2006). Furthermore, drug-cue-related activation of brain circuits in addicts – described as triggering the reward system in an fMRI study by Due et al. (2002) – indicates the importance of emotional valence during the viewing of substance-related cues. The integration of the latter four results with studies showing an increased positivity (400–600 ms) at central sites during recall of emotionally pleasant and unpleasant stimuli in comparison to neutral stimuli in a memory task (Dolcos and Cabeza, 2002), supports the notion that drug-related cues may transport information with high emotional valence possibly triggering networks of motivational behavior. Accordingly, it can be hypothesized that cues, related to the specific drug and addictive consummatory behavior, may influence cognitive behavior in any behavioral context. Depending on a stimulus category-related context these cues might have positive or interfering effects. Confirmatively, interference effects were found in pathological gamblers (McCusker and Gettings, 1997) and in alcohol addicts (Stetter et al., 1994) while using addiction-cue-word-information within a word–color-matching task.

1.4. Current study

In the present study, the influence of direct (primary) and more indirect (secondary) smoking-related compared to neutral monochromatic pictures within a simple color matching task was examined in smokers and non-smokers. Integrating the above cited findings, this study focused on investigating possible group-specific modulatory influences of drug-related cues on early (around 100 ms according to Fehr et al., 2006), middle (between 200 and 300 ms according to Warren and McDonough, 1999) and late (after 400 ms for interference effects according to Markela-Lerenc et al., 2004, drug-cue-related effects according to Warren and McDonough, 1999, and/or emotional aspects according to Dolcos and Cabeza, 2002) ERP components in smokers compared to non-smokers. In addition, general drug-cue-unrelated ERP differences as have been reported for a reduced posterior P300 should be obtained for smokers (Anokhin et al., 2000; Ilan and Polich, 1999). It was hypothesized that the expected drug-cue-related ERP group differences should be reflected in longer reaction times and higher error rates in smokers during a color matching task of smoking-related compared to neutral monochromatic pictures, because of group-specific interference processing.

2. Materials and methods

2.1. Participants

Thirty-four healthy right-handed participants met the inclusion criteria of the study and gave informed and written consent to participate in an approximately 3 h lasting experimental session. The study protocol was designed and performed according to the World Medical Association Declaration of Helsinki (1964). The study sample consisted of 15 smokers (7 male, 26.7 ± 3.9 years, 8 female, 28.0 ± 4.3 years) and 19 non-smoking control participants (8 male, 25.0 ± 2.3 years, 11 female, 24.2 ± 2.0 years), who did not report previous mental illness and psychotropic medication. Except nicotine in smokers, no further exceptional drug use was reported by smokers and non-smokers. Smokers were screened for smoking history (cigarettes per day, mean 16.0 ± 7.6 pieces, and duration of smoking career, mean 10.9 ± 4.2 years). Severity of smoking dependency was assessed by the Fagerstroem test (Fagerstroem and Schneider, 1989; FTND mean 3.0 ± 2.77). Handedness was assessed by a modified version of the Edinburgh Handedness Questionnaire (Oldfield, 1971). Smokers were not nicotine deprived and smoked regularly, according to their habits, before the measurement preparations. That means that the smokers did not smoke at least 45 min before the EEG recordings started.

2.2. Stimuli and procedure

Monochromatic smoking-related and neutral pictures in four different colors (red, green, yellow and blue) were used as stimuli within a color matching task. The task included pictures of two smoking-related picture categories and one neutral stimulus category with the following definition and number of trials per category: 1) 180 primary smoking-related pictures that were directly related to smoking (e.g., cigarettes, ashtrays, hand holding a cigarette, etc.), 2) 180 secondary smoking-related pictures, involving situations where smokers normally think about smoking or do smoke (e.g., train station, bus stop, pubs, etc.), and 3) 260 neutral pictures that were not expected to influence smokers or non-smokers' behavior during color matching (e.g., flowers, buildings, tools, etc.). Stimulus motives were obtained by interviewing twenty smokers and controls, who did not participate in the study. The smokers made suggestions about smoking-related and non-smoking-related picture motives and the suggested motives were then included in the study design.

Participants (sitting in a dimly lit room facing a monitor placed at 75 cm distance from the eyes) were asked to ignore the content of the pictures and only press one of four buttons on a standard computer keyboard (left and right index and middle fingers using the keys "d", "f", "j" and "k") corresponding to the color of the presented monochromatic picture stimulus. Fig. 1 illustrates the design. Four colored rectangles placed below the picture indicated the position of the button representing the target color. The position of the colored rectangles changed every trial to ensure that subjects actively select a color and do not only perform color–motor responses. The intertrial interval was 2 s (trial elements and presentation, see Fig. 1, upper part).
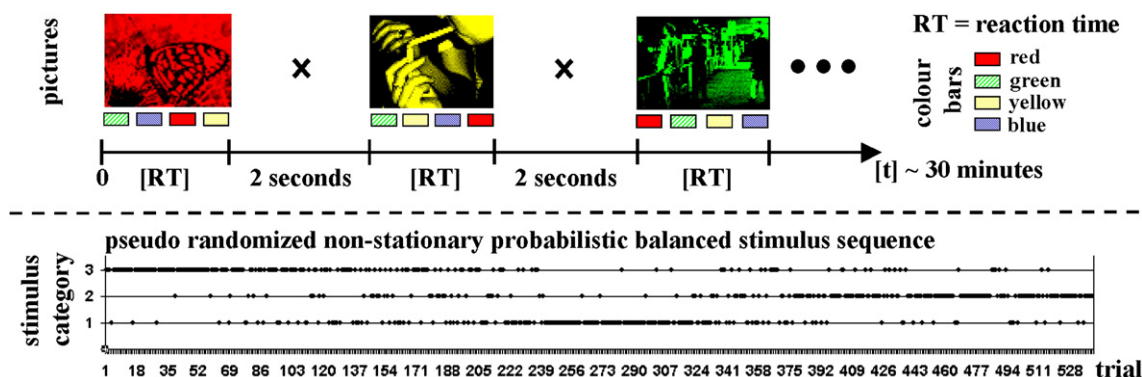

Fig. 1. Upper part: study design; participants had to press a button according to the color bar representing the color of the stimulus; lower part: sequence of stimulus presentation.

Stimuli were presented in a pseudo-randomized non-stationary probabilistic sequence (Friston, 2000). Emotionally valent stimuli have been shown to take effect on subjects over half a minute and more (Garrett and Maddock, 2001) and, therefore, a probabilistic weighted distribution of the different stimulus categories were chosen (trial presentation sequence, see Fig. 1, lower part). The stimuli were presented using the software "Presentation" (Neurobehavioral Systems, Inc., Albany, USA) with a visual angle below 3.8° vertical and horizontal.

2.3. ERP recording and averaging

EEG data was recorded from 19 scalp electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2 placed according to the international 10–20 system; 200 Hz sampling rate; band-pass filter .1–70 Hz; average referenced (each electrode against the average of all others, except of Fp1 and Fp2); impedances around 10 or below 50 kΩ, respectively ($\sim$10 kΩ for all electrodes included in the statistical analyses and average referencing); Nihon Kohden Systems, Neurofax, EEG 9110). Data were processed with BESA (BESA, MEGIS Software, Munich Germany) software for ERP averaging procedures and self developed tools based on Matlab (Math-Works, Inc.; Aachen, Germany) for calculating mean amplitudes over selected time windows.

Only sweeps free of artifacts (extracted by visual inspection) were used for averaging. For eye artifact detection no extra EOG electrodes were placed. Instead, the following procedure was applied. During the first run of the session, subjects were asked to systematically move their eyes (20 blinks and 20 eye movements left, right, up and down each). Eye movements were averaged separately for blinks and each movement direction and the resulting topographies were used as prototypic templates for a spatio-temporal correlation with the EEG data. The resulting correlation curves served as an indirect EOG and indicator for sweep rejection during visual data inspection before sweeps were accepted for averaging. For stimulus-locked analyses data of each stimulus category were separately averaged 500 ms pre- to 1200 ms post-stimulus onset.

According to our hypotheses, we visually inspected ERP curves around 100, between 200 and 300 and between 400 and 600 ms for appropriate margins to define the time windows to be examined. This was done to avoid amplitude averaging over positive and negative parts of the ERP curves. Mean amplitudes of the selected time windows were calculated.

2.4. Data analyses

General linear models repeated measure ANOVAs, using type III sums of squares because of unequal *n* in both groups, were performed on behavioral data (reaction times: between
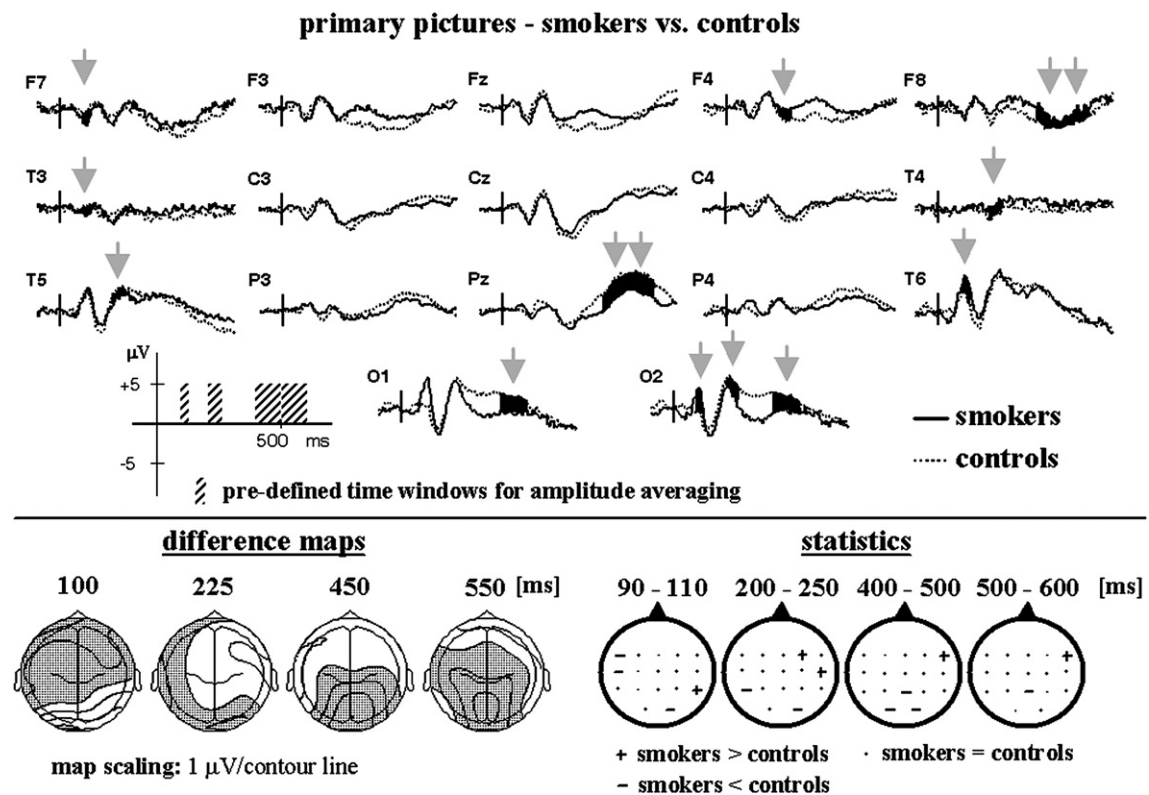

Fig. 2. Upper part: ERPs for smokers and controls (color matching of primary smoking-related pictures); lower left part: corresponding potential maps: top view (100, 225, 450 and 550 ms post-stimulus); back of the head is below; white areas represent positive and shaded areas negative polarity (average referenced); map scaling: 1 µV/contour line. Difference map = smokers–controls; lower right part: significant group differences (post hoc tests for 17 channel positions and four time windows (mean amplitudes); *p* < .05).

subject factor GROUP, 2 levels, within subject factor STIMU-LUS CATEGORY, 3 levels) and mean amplitude values obtained from ERP data (between subject factor GROUP, within subject factors STIMULUS CATEGORY and CHANNELS, topographical analyses see below) using Statistica® (StatSoft, Inc., Tulsa, USA). STIMULUS CATEGORY and CHANNEL variables were treated as repeated measurement factors and the GROUP variable as independent factor. Post hoc analyses (Fisher's LSD, least significant difference tests) were calculated according to the main ERP effects. Scalp distribution analyses were performed on mean amplitudes of different time windows including the electrode positions F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4 and P8. These electrode positions are distributed approximately equidistant and, therefore, appropriate for topographical analyses. From the outset Fp1 and Fp2 were excluded from all analyses because of their particular sensitivity to eye movements. General linear models including the factors GROUP (independent factor, 2 levels), STIMULUS CATEGO-RY (repeated measurement factor, 3 levels), AP (anterior–posterior: frontal, central and posterior channels, repeated measurement factor, 3 levels) and LAT (laterality: repeated measurement factor, 5 levels from left to right electrode sites) were performed using Greenhouse–Geisser adjustments. We report uncorrected degrees of freedom, epsilon values, and adjusted p-values. Group differences for the electrode positions O1 and O2 were examined separately using least significant difference tests (Fisher's LSD). According to Urbach and Kutas

(2002) and Haig et al. (1997) no normalization of EEG signals was performed in the present study because normalization procedures have been shown to unnecessarily distort the signals and even eliminate real differences.

2.5. Multivariate non-parametric permutation tests and omnibus statistics

Because of the large number of variables and statistical dimensions, we calculated non-parametric permutation tests (see Galan et al., 1997) using the statistical software NPC 2.0 (non-parametric permutation test: http://www.methodologica.it, Methodological srl, 2001; Pesarin, 2001; Potter and Griffiths, 2006). To substantiate regional and stimulus category- as well as latency-related group effects, we tested the following models: (1) Assuming that each component in ERPs represent a qualitatively different neural process, we firstly tested the model GROUP (as independent factor, 2 levels)×STIMULUS CATEGORY (as a stratification variable, 3 levels)×ELECTRODE POSITION (as repeated measurement factor, 15 levels) for each time window separately. (2) In two further models we tested regional effects across time windows for anterior–posterior (GROUP (as independent factor, 2 levels)×STIMULUS CATEGORY (as a stratification variable, 3 levels)×ELECTRODE POSITION (as repeated measurement factor, 3 levels: Fz, Cz and PZ)× TIME WINDOW (as second stratification variable, 4 levels)) and laterality effects (GROUP (as independent factor, 2
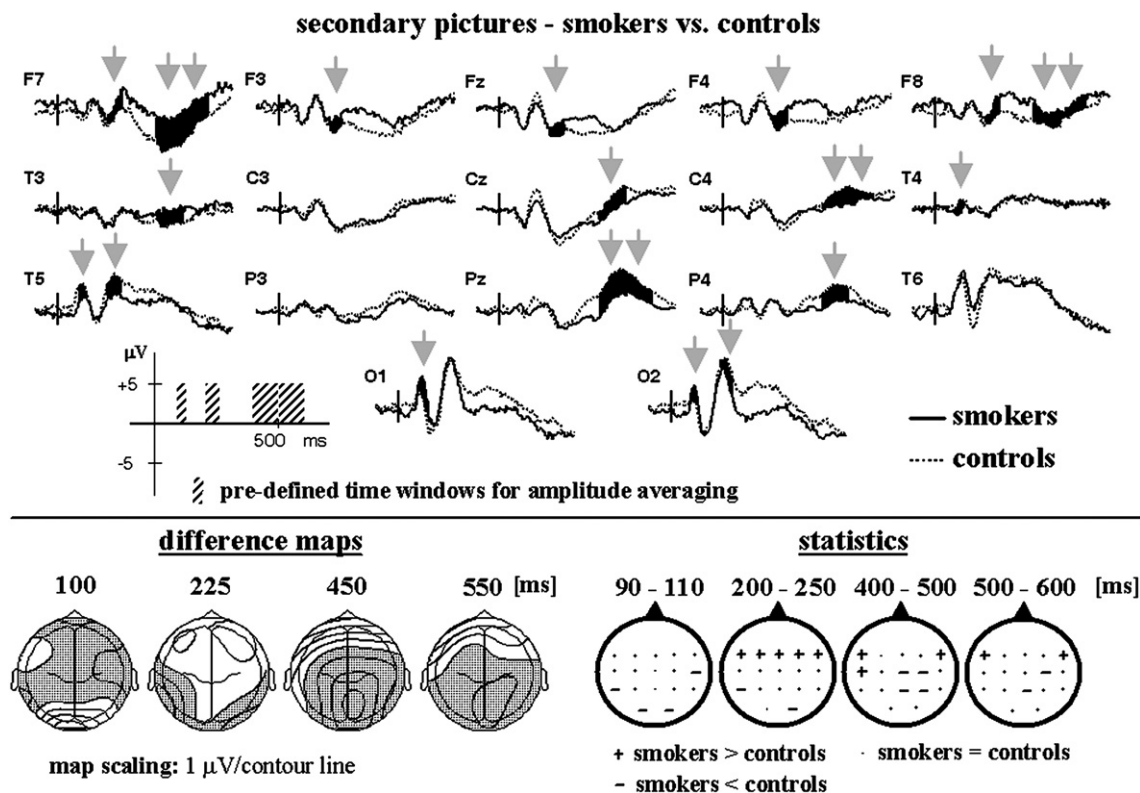

Fig. 3. Upper part: ERPs for smokers and controls (color matching of secondary smoking-related pictures); lower left part: corresponding potential maps: top view (100, 225, 450 and 550 ms post-stimulus); back of the head is below; white areas represent positive and shaded areas negative polarity (average referenced); map scaling: 1 µV/contour line. Difference map = smokers−controls; lower right part: significant group differences (post hoc tests for 17 channel positions and four time windows (mean amplitudes); $p < .05$).

levels)×STIMULUS CATEGORY (as a stratification variable, 3 levels)×ELECTRODE POSITION (as repeated measurement factor, 6 levels with pooled positions F7 and F3, F4 and F8, T7 and C3, C4 and T8, P7 and P3, P4 and P8)×TIME WINDOW (as second stratification variable, 4 levels)).

3. Results

3.1. Behavioral data

There were no significant differences between smokers and non-smokers with respect to reaction times in any experimental stimulus category. Primary smoking-related pictures showed longer reaction times compared to all other stimulus categories ($F(3,96)=22.9$, $p<.001$ (Greenhouse–Geisser: $p<.001$, $\varepsilon=.71$; Wilks-Test for main effect STIMULUS CATEGORY: $F(2,31)=4.2$, $p<.05$). Error rates were below 5% for all stimulus categories and, therefore, not further analyzed in detail.

3.2. ERP data

For each participant and for each stimulus category (i.e., neutral, primary and secondary smoking-related pictures) a comparable number of artifact-free sweeps were used for averaging. The upper part of the Figs. 2 and 3 illustrates the ERPs elicited by the primary and secondary smoking-related pictures in smokers and non-smokers. The ERPs for the neutral

stimulus category in smokers and non-smokers are presented in Fig. 4. Topographical analyses (including the repeated measurement factors "anterior–posterior electrode positions (AP)", "left to right side electrode positions (LAT)", STIMULUS CATEGORY, and GROUP as independent factor) confirmed regional stimulus category-related and/or group-specific differences for the time windows 90–110 ms, 200–250 ms, 400–500 ms and 500–600 ms (summarized in Table 1). Figs. 2, 3 and 4 illustrate post hoc tests at the lower right panel. Results were only considered for discussion when significant at a 5% level. All effects that are discussed in the Discussion section were additionally verified by multivariate non-parametric (see last paragraph of the Results section) tests.

Main stimulus category-related regional differences can be summarized as follows: When compared to neutral stimuli, primary smoking-related pictures showed a relative positivity over right posterior electrode sites (O2, T6) between 200 and 250 ms. Color matching of secondary smoking-related pictures showed a relative negativity at frontal and central electrode sites and a relative positivity at posterior and posterio-temporal electrode sites between 200 and 250 ms compared to neutral pictures. Furthermore, secondary smoking-related pictures showed a right fronto-temporal relative positivity (F8, T4) between 400 and 600 ms and a left frontal relative negativity between 400 and 500 ms at F7.

Smokers and controls differed irrespective of the experimental stimulus categories at several electrode positions.
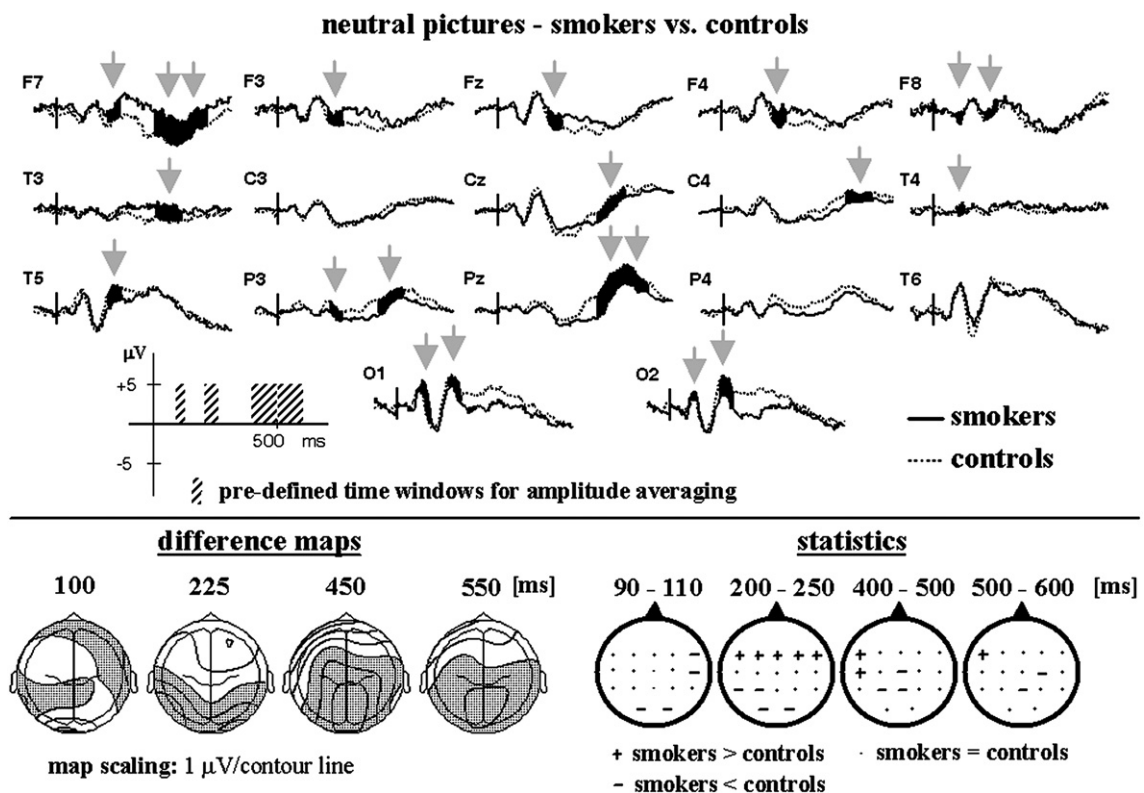

Fig. 4. Upper part: ERPs for smokers and controls (color matching of neutral pictures); lower left part: corresponding potential maps: top view (100, 225, 450 and 550 ms post-stimulus); back of the head is below; white areas represent positive and shaded areas negative polarity (average referenced); map scaling: 1 μV/contour line. Difference map = smokers–controls; lower right part: significant group differences (post hoc tests for 17 channel positions and four time windows (mean amplitudes); $p<.05$).

Table 1
ERP statistics: time window [ms]; factors (AP = anterior–posterior and LAT = left- to right-sided electrode positions, STIMULUS CATEGORY (SC), and GROUP); uncorrected degrees of freedom [df]; F-value; significance level [p]; Greenhouse–Geisser Epsilon (ε); Greenhouse–Geisser corrected p-value

Statistics						
[ms]	Factors	df	F	p	ε	GG
Regional GROUP × SC						
90–100	AP × LAT × SC × GROUP	16, 480	1.8	<.05	.51	.08
200–250	AP × SC × GROUP	4, 120	3.8	<.01	.72	<.05
400–500	AP × LAT × SC × GROUP	16, 480	2.4	<.01	.40	<.05
500–600	AP × LAT × SC × GROUP	16, 480	1.8	<.05	.46	.08
Regional GROUP						
400–500	AF × GROUP	2, 60	4.7	<.05	.63	<.05
400–500	LAT × GROUP	4, 120	4.4	<.01	.37	<.05
500–600	LAT × GROUP	4, 120	4.6	<.01	.44	<.05
Regional SC						
90–110	AP × SC	4, 120	2.5	<.05	.61	.07
200–250	AP × SC	4, 120	4.9	<.01	.72	<.01
200–250	LAT × SC	8, 240	4.8	<.01	.58	<.01
200–250	AP × LAT × SC	16, 480	1.8	<.05	.48	.08
400 – 500	LAT × SC	8, 240	2.9	<.01	.49	<.05
500 – 600	AP × SC	4, 120	2.6	<.05	.64	.06
500 – 600	LAT × SC	8, 240	2.2	<.05	.43	.08
Regional						
90–110	AP	2, 60	34.1	<.01	.61	<.01
90–110	LAT	4, 120	26.6	<.01	.63	<.01
90–110	AP × LAT	8, 240	12.5	<.01	.41	<.01
200–250	AP	2, 60	11.5	<.01	.56	<.01
200–250	LAT	4, 120	33.8	<.01	.61	<.01
200–250	AP × LAT	8,240	14.8	<.01	.55	<.01
400–500	AP	2, 60	41.0	<.01	.63	<.01
400–500	LAT	4, 120	6.0	<.01	.37	<.01
400–500	AP × LAT	8, 240	4.7	<.01	.55	<.01
500–600	AP	2, 60	12.6	<.01	.65	<.01
500–600	LAT	4, 120	34.8	<.01	.44	<.01
500–600	AP × LAT	8, 240	25.6	<.01	.64	<.01

Prominently between 90 and 110 ms (at O2), between 200 and 250 ms (at O2, T5) and between 400 and 600 ms (at Pz) smokers showed a posterior relative negativity compared to non-smokers.

Group differences related to the primary and secondary smoking-related and neutral pictures were mainly characterized by smokers showing a reduced posterior positivity (or relative negativity) slightly varying with the stimulus category at different electrode sites. Figs. 2, 3 and 4 (lower left panels for group difference maps and lower right panels for statistical details) illustrate that during 200 and 250 ms smokers in comparison to non-smokers showed a prominently right frontal relative positivity (or reduced negativity) for primary smoking-related pictures and a broad frontal relative positivity (or reduced negativity) for the secondary smoking-related and neutral picture category. Furthermore, during 400 and 600 ms smokers showed a relative frontal positivity (or reduced negativity) right lateralized for primary and bilaterally for secondary smoking-related and left lateralized for neutral pictures in comparison to non-smokers. Figs. 2, 3 and 4 show further statistical details and differences maps.

3.3. Multivariate non-parametric permutation tests and omnibus statistics

Multivariate non-parametric permutation tests for each defined time window (GROUP (as independent factor, 2 levels) × STIMULUS CATEGORY (as a stratification variable, 3 levels) × ELECTRODE POSITION (as repeated measurement factor, 15 levels)) confirmed regional stimulus category-related group differences for the latency ranges 200–250 (p<.05), 400–500 (p<.05) and 500–600 ms (p<.05) using Fisher's combining function. Time window related regional and stimulus category-related group differences obtained by parametric tests were substantiated by significant anterior–posterior (GROUP (as independent factor, 2 levels) × STIMULUS CATEGORY (as a stratification variable, 3 levels) × ELECTRODE POSITION (as repeated measurement factor, 3 levels: Fz, Cz and PZ) × TIME WINDOW (as second stratification variable, 4 levels); p<.01) and lateral (GROUP (as independent factor, 2 levels) × STIMULUS CATEGORY (as a stratification variable, 3 levels) × ELECTRODE POSITION (as repeated measurement factor, 6 levels with pooled positions F7 and F3, F4 and F8, T7 and C3, C4 and T8, P7 and P3, P4 and P8) × TIME WINDOW (as second stratification variable, 4 levels); p<.05) regional analyses. Regional differences at different electrode positions as resulted from parametric least significance tests were confirmed by non-parametric permutation (omnibus) test procedures.

4. Discussion

The present study investigated influences of drug-related cues on ERP generation in smokers and non-smokers. We employed a simple color matching task including different stimulus categories using monochromatic primary and secondary smoking-related pictures and pictures with neutral content. In addition to suggested general ERP differences between smokers and non-smokers, a group-specific, possibly emotionally driven, drug-cue-related modulation of brain activation in smokers compared to non-smokers was hypothesized in relation to the smoking-related stimuli. These general hypotheses were supported by the present data. Apart from general ERP differences between smokers and non-smokers the smoking-related stimuli appeared to produce additional specific ERP differences.

Behavioral data showed the expected interference effect on color matching only for primary smoking-related pictures, but for both smokers and non-smokers. Moreover, physiological data in both smokers and control participants showed regional stimulus category-specific and stimulus category-independent group differences during color matching of primary and secondary smoking-related pictures compared to neutral pictures. Smokers in comparison to non-smokers showed a generally stimulus category-independent reduced posterior positivity (consistently at Pz) electrode sites during later latencies most prominent between 400 and 500 ms. This finding is complementary to studies showing a generally reduced visual P3b in smokers compared to controls and ex-smokers (Anokhin et al., 2000; Ilan and Polich, 1999; Polich and Ochoa, 2004; Polich and Criado, 2006).

Furthermore, the data suggest that there are differences between the smokers and non-smokers in the processing of the primary and secondary smoking-related picture motives, which may result from differences in cognitive processing and/or emotional valence. Contents of the primary smoking-related pictures seem to interfere the color matching process in both groups, but the interference appears to be related to different factors. For primary smoking-related picture stimuli the relative pronounced late frontal positivity in smokers compared to control participants tended to right frontal and fronto-temporal regions, and for secondary smoking-related and neutral picture stimuli to left fronto-temporal electrode sites. These results partially reflect what we hypothesized in the introduction. For smokers, we expected a stimulus category-related modulation of ERPs at late latencies after 400 ms. This amplitude effect can be assumed to be associated with a potential cue interference effect (Warren and McDonough, 1999), which might on its part be intensified by a positivity elicited by the group-specific emotional valence of the nicotine cues as reported analogously for emotional stimuli (Dolcos and Cabeza, 2002). Similar group-specific stimulus category-related effects for word stimuli were shown in ERP topographies in a previous study by Fehr et al. (2006), which indicates that the activation patterns might be elicited by the semantic content and not by special features of the tasks, such as pictures or words used as stimuli.

As mentioned above, chronic nicotine consumption has been shown to generally lead to changes in late ERP component generation. However, these findings and their interpretation do not appear fully sufficient to explain why the present data show group-related late regional frontal ERP modulation in smokers compared to non-smokers in relation to smoking-related and neutral pictures. All the interpretations, inferred by the results of this study, should be evaluated considering possible pharmacodynamic interaction effects with nicotine metabolism, because smokers were not nicotine deprived and smoked regularly, according to their habits, before the examination. Nevertheless, aspects such as deprivation effects, usually related to P300 reduction (Polich and Ochoa, 2004), or acute nicotine effects, suggested to be related to increases in P3a and P3b components when comparing nicotine intake with placebo treatment, cannot fully explain the present results (Polich and Criado, 2006), given, that the pre-test deprivation time was too short to induce craving and too long to argue solely for an acute nicotine effect on the ERP differences (Pritchard, 1991; Domino and Matsuoka, 1994; Haarer and Polich, 2000). The present data at least indicate an interaction between general changes due to smoking status and smoking-related stimulus content.

4.1. Interference induced by smoking-related cues in both smokers and non-smokers

Right frontal brain activity enhancement has been discussed with respect to withdrawal and/or inhibitory behavior, and left frontal activation is suggested to be related to appetitive approaching behavior, as reported by Davidson and Irwin (1999) and Davidson et al. (2000). The pronounced relative right frontal positivity (or reduced negativity) in smokers related to primary smoking cues might possibly reflect an emotionally driven inhibitory process which interferes with the color matching of the stimuli. Esslen et al. (2004) reported right lateralized pre-frontal EEG source space activity based on low resolution electromagnetic activity (LORETA) estimations in different epochs between 50 and 500 ms post-stimulus associated with different induced moods by emotional facial expression processing. Furthermore, Norton et al. (1992) reported a nicotine dose related higher right hemispheric brain activation. Combining those findings, primary smoking-related stimuli are possibly associated stronger and directly with smoking and, therefore, with an expected nicotine flooding that enhances right hemispheric brain activity, as indicated by the relatively stronger positivity in the smoker group. Stimulus induced emotional states and learned contingencies between smoking and effects of nicotine flooding might underlie the observed stimulus-related right hemisphere shift of the relatively higher right frontal positivity in the smoker group.

The modulation of frontal brain activity – possibly due to emotional processing and/or "nicotine intake expectation" – did not reduce the cognitive performance exclusively in the smoker group. In former studies smoking has been shown to enhance or normalize cognitive performance in smokers (Kumari et al., 2003; Lawrence et al., 2002; Pritchard et al., 1995; and others). Additionally, smoking-related cues activated similar brain regions as seen during real smoking (Stein et al., 1998). Thus, it might be that the hypothesized influence on cognitive processing, that was expected to be found in form of increased reaction times and error rates, might be to some extent counteracted by the stimulating effect of the smoking-related cues.

4.2. Functional integration of memory and action

Taking into account that there were no reaction time differences between groups, different group-specific emotional and/or cognitive processes elicited the by the different stimulus categories during the task must be interpreted rather in terms of parallel than sequential processing. Gray et al. (2002) found bilateral pre-frontal regions that were only activated by emotionally induced states combined with cognitive demands but not during *either* only emotional *or* only cognitive processing. This finding suggests that there are brain regions that integrate emotional and cognitive aspects of behavior. Such an integrative form of functional and/or anatomical association between emotional and cognitive aspects of behavior, especially in frontal brain regions, gave rise to the assumption that emotional aspects of situations could be directly linked to complex behavior-related engrams and, therefore, to direct behavior. Stable engrams or networks subserving, e.g., addiction memory networks might result in enhancing the effort for addicted persons to avoid drug consumption behavior, which is "guided" by emotional processes like craving. The theory of integrating "perception–action cycles" in behavior (Fuster, 2006; Basar, 2005, 2006) which have been discussed to include constant reciprocal activations based on an alliance of subprocesses of attention, perception, learning and remembering (Basar, 2004, 2005) would support such an idea. It has been suggested that all cognitive brain functions are inseparable, e.g., from memory

and perceptual functions, and that the units and their interplay can be observed as responsiveness of the brain, and measured as modulations in ERP parameters (Basar, 2005, 2006; Basar et al., 2000). The present data support this idea.

4.3. Linking the present ERP differences with neuropharmacological implications

Nicotine receptors have been reported to be widely distributed in cortical, hippocampal regions and the nucleus accumbens (for an excellent review concerning the relationship between the P3 and the transmitter systems, see Polich and Criado, 2006). Furthermore, nicotine is strongly involved in dopamine metabolism as it regulates dopamine release by modulating the impulse flow to nerve terminals (Wonnacott, 1997; Jones and Benowitz, 2002), and dopamine plays an important role in stimulant and rewarding aspects of behavior. The degree of nicotine consumption, as well as alcoholism risk have been suggested to be related to a possible genetic predisposition for dopamine system deficits, which in turn have been thought to encourage drug use (e.g., Polich and Ochoa, 2004). Moreover, it has been suggested that the P300 underlying generator system is mediated by catecholaminergic transmitter systems (e.g., Hansenne et al., 1995; Polich and Ochoa, 2004). Polich and Criado (2006) discussed a relationship of a frontal distributed P3a in relation to the dopamine system and a posterior distributed P3b in relation to the locus coeruleus norepinephrine transmitter system. Whereby, the P3a results when a demanding stimulus commands frontal lobe attention, and the P3b is produced when attention resources are allocated for memory updating in association cortex. Thus, the here observed frontal stimulus category-modulated relative positivity in smokers can at most be defined as P3a-like. But nevertheless, it appears reasonable to speculate that the anterior smoking cue-related relative positivity between 400 and 600 ms in smokers compared to non-smokers in the present study, might indicate that the stimulus content modulates frontal dopaminergic transmission, similar to acute nicotine consumption. Thereby, this process might trigger reward expectancy and motivational behavior related to drug consumption. Physiological evidence for an enhanced liability to involuntary attention shifts in alcohol addicts has been shown in an ERP study by Polo et al. (2003). Given this effect, the influence of individual drug cues should be taken into account during treatment interventions. In addition to the assessment of genetic predisposition for smoking (Polich and Ochoa, 2004), information on the influence of situative cues related to drug consumption, i.e., addiction memory, should consequently be given.

The examined pre-defined time windows in the present study might possibly not reflect the whole process discussed. It seems, after visual inspection of the ERP curves, that the time window between 300 and 400 ms might also contribute to ERP-related group differences between smokers and non-smokers. More precisely, this might be the case at mid-frontal electrode positions as reflected in a relative reduced negativity (or relative positivity) and at occipital electrode positions reflected as a relative negativity for smokers in comparison to non-smokers. However, these differences seem to be present for each picture category, and thus, putatively would not influence the discussion about the picture category-related group differences. The time window between 300 and 400 ms should hypothetically be considered in future studies, at least when investigating general ERP group differences between smokers and non-smokers.

The central presented group differences can be interpreted as further evidence for the concept of an addiction memory in smokers. Relationships between emotional and cognitive processing were discussed as possibly being highly interwoven and influencing each other in a "reflexive" way. These processes may be triggered by learned environmental cues embedded in the introductory assumed "perception–action cycles" and potentially influence relapse into addiction. Nevertheless, more studies and investigations are needed on this topic, including variable populations of participants, stimulus/task parameters, and smoking history, as well as investigations on spatio-temporal brain dynamics using advanced methods, such as combined biosignal analysis and imaging methods.

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