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Neural responses to BEGIN- and END-stimuli of the smoking-ritual in non-smokers, non-deprived smokers and deprived smokers

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Abstract

Drug associated stimuli (cues) play a prominent role in addiction research because they are able to provoke craving and relapses. Generally, drug cues are seen as conditioned excitatory stimuli, which elicit drug seeking and usage. However, newer data suggest differential effects for smoking stimuli depending on their stage in the smoking ritual. Specifically, stimuli associated with the terminal stage of smoke consumption (END-stimuli) may evoke reactivity opposite to the reactivity evoked by stimuli associated with the beginning of smoke consumption (BEGIN-stimuli).

This fMRI-study compared twenty non-deprived smokers with 20 non-smokers to unravel the influence of smoking related pictures displaying the beginning (BEGIN-stimuli) and termination (END-stimuli) of the smoking ritual on neural activity in the addiction network. Additionally, 20 deprived smokers (12 h deprivation) were investigated to explore the effects of deprivation on the processing of these stimuli.

In non-deprived smokers, BEGIN-stimuli reliably activated the addiction network (e.g. ventral striatum, orbitofrontal cortex, anterior cingulate cortex). In contrast, END-stimuli triggered a differential pattern of activations as well as deactivations; deactivations were found in the ventral striatum and the ACC. Deprivation had no clear effect on the responses triggered by BEGIN-stimuli, but affected the reactivity to END-stimuli.

Our data clearly suggest that stimuli associated with different stages of the smoking-ritual trigger differential neuronal responses. While BEGIN-stimuli generally seem to activate the addiction network, END-stimuli presumably have some inhibitory properties. This new finding might add to a more differentiated understanding of cue-reactivity and addiction.

Keywords: addiction, smoking, cue-reactivity, fMRI, deprivation, terminal stimuli

Introduction

Core features of addiction are excessive craving, compulsive drug intake and high rates of relapse (Self and Nestler, 1998; Kalivas and Volkow, 2005; Lubman *et al*, 2004). Current learning theories of addiction emphasize the prominent role of drug cues - stimuli associated with drug intake, which may induce craving, lapses and relapses (Wikler, 1948; Siegel, 1989; Stewart *et al*, 1984; Robinson and Berridge, 1993, 2003). Empirical data support these assumptions for smokers and smoking cues (Carter and Tiffany, 1999; Niaura *et al*, 1988; O'Brien *et al*, 1998).

Brain research confirmed that addiction is a disorder of learning and memory (Kauer and Malenka, 2007; Hyman, 2005; Everitt *et al*, 2001). Evidence suggests that drugs lead to pathological adaptations in a widely distributed neuronal network divided into four sub-circuits: reward/salience (ventral tegmental area, ventral striatum); motivation/drive/craving (orbitofrontal cortex, insula); learning/memory (hippocampus, amygdala); and control (dorsolateral prefrontal cortex, anterior cingulate cortex) (Everitt and Robbins, 2005; Volkow *et al*, 2003, 2004; Naqvi and Bechara, 2009). Smoking cues were found to activate this network in smokers but not in non-smokers (Due *et al*, 2002; David *et al*, 2005; Brody *et al*, 2002; Smolka *et al*, 2006; Franklin *et al*, 2007).

However, stimuli associated with different stages of the smoking-ritual seem to trigger differential responses. Using pictures of different stages of smoking, Mucha *et al* (1999, 2008) found evidence that pictures representing the beginning and the process of smoking (BEGIN-stimuli, e.g. scenes of lighting a cigarette) elicit high craving. Pictures representing the terminal phase of smoking (END-stimuli, e.g. scenes of the disposal of a finished cigarette) elicit low craving, although they are

associated with a high nicotine level in the body (see also Bushnell *et al*, 2000). A difference was also demonstrated using a physiological measure of motivational state: contrary to END-stimuli, BEGIN-stimuli attenuate the startle-response similar to positive pictures (Geier *et al*, 2000; Mucha *et al*, 2008; Mucha *et al*, 2006). However, END-stimuli are probably not simply weak cues since they are able to reduce the effects of BEGIN-stimuli when both are presented together (Mucha *et al*, 2008). Therefore, END-stimuli seem to trigger a unique reactivity, which even may oppose responses triggered by BEGIN-stimuli. Mucha *et al* (2008) suggested this to be an effect of the perceived smoke availability, which is high for BEGIN- and low for END-stimuli. Previous studies demonstrated increased subjective, behavioral, physiological, and neuronal responses to smoking-cues when smoking seems available (Wertz and Sayette, 2001; Carter and Tiffany, 2001; Wilson *et al*, 2004; McBride *et al*, 2006). Other studies showed that the end of drug consumption and stimuli predicting the non-occurrence of the drug reduce drug-seeking and wanting (Kearns *et al*, 2005; see also Panlilio *et al*, 2008). In sum, these results point to an inhibitory nature of END-stimuli.

There are however alternative explanations for the low cue reactivity of END-stimuli (Mucha *et al*, 2008). Therefore, it is important that research on END-stimuli has focused on subjective and physiological responses, but nothing is known about their neuronal representation. Accordingly, this fMRI-study was designed to investigate whether END-stimuli have an impact on neuronal activity in the addiction-network and whether they lead to inhibitory effects. Prototypical BEGIN-("lighting a cigarette") and END-stimuli ("stubbing out a cigarette butt") were presented to non-deprived smokers, deprived smokers (12 h deprivation), and non-smokers. Furthermore, our study included an expansion of the concept of BEGIN- and END-stimuli. Several animal conditioning studies suggest that conditioned stimuli (CS) lead to different

behavioral responses depending on their temporal proximity to the unconditioned stimulus (UCS) (Timberlake, 1997; Silva *et al*, 1996, 1998; Silva & Timberlake, 1997). For example, with food as reinforcer, long CS-UCS intervals lead to general search behavior, whereas short intervals lead to focal search behavior. A similar functional organization may also be present in the smoking-ritual. Thus, we added two exploratory stimuli (“taking a cigarette out of its box”, “the last puff”) to represent a wider range of the smoking-ritual.

Several directional hypotheses were put forward for BEGIN- and END-stimuli: for non-deprived and deprived smokers we hypothesized that BEGIN-stimuli lead to neuronal activations, whereas END-stimuli should result in deactivations. Regarding group differences, we expected that these effects are significantly different between non-deprived smokers and non-smokers. Similar group differences were expected between deprived and non-deprived smokers, because learning theories suggest an enhancement of the incentive-value of drug-associated stimuli under deprivation (Stewart *et al*, 1984; Toates, 1994; Berridge, 2004). We had no directional hypotheses for the effects of the additional stimuli. However, we also expected significant group differences for them.

Method

Subjects

Sixty right-handed subjects participated in the study: 20 non-deprived smokers (11 female), 20 deprived smokers (10 female), and 20 non-smokers (10 female). Non-deprived and deprived smokers were included if they had smoked for at least three years and a mean of at least 15 cigarettes per day in the last 12 months; non-smokers had to have smoked less than 10 cigarettes in their lifetime. The Edinburgh Inventory of Handedness (Oldfield, 1971) ensured that only right-handed subjects participated. A self-generated questionnaire was used to assess general information regarding smoking history. The Fagerström Test of Nicotine Dependence (FTND; Schumann *et al*, 2003a) was used to assess the severity of addiction. Deprived smokers were instructed to go to bed before 12:00 pm the day before the experiment and were scheduled after 12:00 am the day of the experiment. This resulted in a deprivation phase of at least 12 hours. The procedure was the same for non-deprived smokers and non-smokers.

Most subjects were students receiving either money (10 Euro/hour) or course credit. No subject was taking regular medication or had a history of psychiatric or neurological illness. None of the participants reported abuse of other drugs. The study was performed in accordance with the ethical standards of the fifth revision of the Declaration of Helsinki and approved by the Ethical Committee of the German Psychological Association.

Stimulus material

We used self-generated pictures and videos depicting different stages of the smoking-ritual without showing many irrelevant or distracting features (e.g., faces, surroundings, cigarette brands). As neutral controls, stimuli depicting equivalent temporal stages of teeth-brushing were used. Teeth-brushing can be matched to the smoking-process with respect to temporal stages, body parts, and equipment. It can be considered as neutral because it is an over-learned every day routine. All props (e.g., ashtrays, lighters, toothbrushes, beakers) were matched for color.

We recorded 12 video clips using 12 different models (6 female) while smoking or teeth-brushing. We then cut 4 sequences (4 seconds each) out of each clip. Each represented one of four different stages of smoking or teeth-brushing. Then, one representative static picture from each clip was selected. Smoking-stages were: “taking a cigarette out of its box” (S1), “lighting a cigarette” (S2), “last puff on a cigarette” (S3), and “stubbing out a cigarette butt” (S4). Teeth-brushing stages were: “preparing a toothbrush with toothpaste” (T1), “putting a toothbrush into ones mouth” (T2), “taking a toothbrush out of ones mouth” (T3), and “putting a toothbrush back into the beaker” (T4). Overall, eight different picture categories were used, with every smoking-stage having its own teeth-brushing stage as control (S1, S2, S3, S4, T1, T2, T3, T4). Among these stimuli, we focused on S2 and S4, since they are prototypical BEGIN- (S2) and END-stimuli (S4) of smoking. S1 and S3 were considered as exploratory to account for a wider range of the smoking-ritual.

To study differential effects of pictures and video clips, both were presented in separate and counterbalanced sessions on different days one week apart. The data regarding the picture stimuli will be the focus of this paper. Results regarding the video stimuli will be reported separately. All pictures were presented in 800 x 600 pixel resolution. An LCD projector (model EPSON EMP-7250) projected them onto a

screen at the end of the scanner (visual field=18°) where they were viewed through a mirror mounted on the head coil. Pictures were presented for 4 seconds in randomized order (restriction: not more than two stimuli of the same category after one another).

Participants rated the stimuli right after their presentation on the dimensions craving, valence and arousal on 9-point Likert scales using a three-button keypad (left, right, enter). For craving, the scale was visualized with bars of different heights representing the amount of craving. For valence and arousal, a computerized version of the Self Assessment Manikin (SAM; Bradley and Lang, 1994) was applied. Ratings of craving were assessed after each stimulus. Valence and arousal ratings interchanged to keep the experiment short (each stimulus category was rated half on valence and half on arousal).

Procedure

Subjects participated in three different sessions.

Session 1. The study was explained, possible contraindications were checked and written consent was obtained. Smokers were randomly assigned to the non-deprived or the deprived group. All subjects were instructed to go to bed before 12 pm on the days before the experiments (sessions 2 and 3). Deprived smokers were instructed not to smoke from bedtime to the end of the experimental sessions. After reading the instructions, all smokers were told to smoke one cigarette. This was necessary to measure a carbon monoxide (CO)- and craving-baseline (German version of the Questionnaire on Smoking Urges, QSU-G; Müller *et al*, 2001) when non-deprived. CO-values and craving were also assessed in non-smokers. All subjects had to fill in a self-generated questionnaire regarding their individual smoking history. Afterwards,

an anatomical measurement took place in the MRI scanner to get participants accustomed. Afterwards, smokers completed different smoking-related questionnaires (analyses not included).

Session 2 and 3. Each experimental session started between noon and 6 pm. Non-deprived smokers were allowed to smoke one cigarette before the procedure started. Then, all subjects completed a CO-measurement. Subsequently, they filled in the German version of the Questionnaire on Smoking Urges (QSU). CO-levels were used to confirm deprivation. All deprived smokers had CO-levels ≤ 13 CO-ppm, which is similar to the mean value found in other studies with overnight deprivation (Due *et al*, 2002; Della Casa *et al*, 1999; Mucha *et al*, 1999). Next, participants were familiarized with the stimulus-presentation and rating procedure outside the scanner. Only neutral pictures from the International Affective Picture System (IAPS; Lang *et al*, 1995) were presented. Subjects were then placed in the scanner. Another test-rating took place before the experiment. After the experiment all smokers were allowed to smoke. They then filled in personality questionnaires (analyses not included). After completing all sessions, participants were paid and debriefed.

Data acquisition and analysis

Brain images were acquired using a 1.5 T whole-body tomography (Siemens Symphony) with a standard head coil. Structural image acquisition consisted of 160 T1-weighted sagittal images (MPRage, 1 mm slice thickness). A gradient echo field map sequence was measured before the functional run to get information for unwarping B0 distortions. For functional imaging a total of 780 volumes were registered using a T2*-weighted gradient echo-planar imaging sequence (EPI) with 25 transversal slices covering the whole brain (slice thickness = 5 mm; 1 mm gap;

descending; TR = 2.5 s; TE = 55 ms; flip angle = 90°; field of view = 192 x 192 mm; matrix size = 64 x 64). The first three volumes were discarded due to an incomplete steady state of magnetisation. Orientation of slices was parallel to the AC-PC line.

The statistical parametric mapping software package (SPM5, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Inc., Natick, MA, USA, Release 2007b) was used for preprocessing and statistical analyses. Origin coordinates were adjusted to the anterior commissure (AC), and realignment (third order B-spline) and unwarping, slice time correction, and normalization to the standard brain of the Montreal Neurological Institute (MNI) were performed. Smoothing was executed with an isotropic three-dimensional Gaussian filter with a full width at half maximum (FWHM) of 9 mm.

For the event-related design, each picture presentation was modeled with a box-car function convolved with a hemodynamic response function (duration 4 s) in the General Linear Model of SPM. The six movement parameters of the rigid body transformation applied by the realignment procedure were introduced as covariates in the model. The serial correlation in the voxel-based time series was considered as a first order autoregressive process. A high pass filter (time constant = 128 s) was implemented by using cosine functions in the design matrix.

For analyses of hemodynamic responses, contrasts between smoking and corresponding control stimuli (smoking minus control) were calculated on the first level: S1-T1 is called TAKING OUT, S2-T2 BEGIN, S3-T3 LAST PUFF, and S4-T4 END. These contrasts were then used as dependent variables on the second level. Activations were defined as positive differences between smoking and control stimuli; deactivations as negative differences. The second level model was a variance analytical model with the factors *group* and *stage* (four stages). Our data analysis comprised a confirmatory part and an exploratory part: in the confirmatory part,

appropriate contrasts for each hypothesis were constructed within this model and T-tests were applied to these contrasts. Group comparisons (non-deprived smokers vs. non-smokers; deprived smokers vs. non-deprived smokers) were done for 1) BEGIN-stimuli, 2) END-stimuli and 3) differences between BEGIN- and END-stimuli. Afterwards, exploratory analyses were performed by comparing the groups (non-deprived smokers vs. non-smokers; deprived smokers vs. non-deprived smokers) for all four smoking stimuli in two 2 by 4 plans.

Regions of interest (ROI) analyses were performed for: dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), ventral tegmental area (VTA), ventral striatum, amygdala, hippocampus, and insula. Results were corrected for multiple testing in each ROI according to Worsley (2001).

Ratings were analyzed with SPSS 17.0. The analysis was analogous to that of the brain data but without computing differences between smoking and control stimuli beforehand. For the repeated measure factor *stage*, the Greenhouse-Geisser correction was applied. Post hoc comparisons were performed using the Bonferroni-adjustment for multiple comparisons. For all statistical analyses α was set to .05.

Results

Group characteristics

The final analyses are based on 20 deprived smokers (10 female), 19 non-deprived smokers (11 female), and 17 non-smokers (9 female). Four subjects had to be excluded: one smoker and one non-smoker due to technical problems and two non-smokers because they had smoked more than 10 cigarettes in their lifetime. Table 1 summarises relevant group characteristics.

As intended, the groups did not differ in age. Non-deprived smokers and deprived smokers did not differ in years smoked, mean number of cigarettes per day within the last 12 months and FTND-score. As expected, the three groups differed in craving and CO-levels at baseline measured in session 1 (QSU-baseline: $F(2, 52) = 26.261$, $p < .001$; CO-baseline: $F(2, 53) = 39.694$, $p < .001$). Craving scores and CO-levels were higher in non-deprived smokers and deprived smokers than in non-smokers (QSU-baseline: non-deprived smokers vs. non-smokers: mean difference = 1.33, $p < .001$, deprived smokers vs. non-smokers: mean difference = 1.71, $p < .001$; CO-baseline: non-deprived smokers vs. non-smokers: mean difference = 25.73, $p < .001$, deprived smokers vs. non-smokers: mean difference = 25.66, $p < .001$). On the day of the scanning session, deprived smokers showed higher craving scores ($t(37) = 7.740$, $p < .001$) and lower CO-levels ($t(37) = -8.585$, $p < .001$) than non-deprived smokers. They also had significantly higher craving scores and lower CO-levels than at baseline (QSU: $t(19) = 7.976$, $p < .001$; CO-levels: $t(19) = -8.386$, $p < .001$). Thus, CO- and QSU-levels confirmed the effectiveness of the deprivation manipulation.

--- insert Table 1 ---

Picture ratings for BEGIN- and END-stimuli

The following section focuses on the rating data for smoking stimuli (differences to control stimuli, differences to other smoking stimuli, group differences). Differences with regard to control stimuli (differences to other control stimuli, group differences) are not reported in the text but can be seen in Table 2.

Non-deprived smokers compared to non-smokers

Craving (Figure 1, Table 2). In non-deprived smokers, BEGIN- and END-stimuli led to more craving than the corresponding control stimuli (BEGIN: $t(18)=4.40$, $p<.001$; END: $t(18)=2.57$, $p=.019$). BEGIN-stimuli led to higher craving than END-stimuli ($t(18)=4.22$; $p=.001$). For non-smokers, no significant results were found. Comparing both groups, non-deprived smokers revealed higher craving ratings than non-smokers for BEGIN- and END-stimuli (BEGIN: $t(18)=6.96$, $p<.001$; END: $t(18)=6.63$, $p<.001$).

--- insert Figure 1 ---

Valence (Table 2). Non-deprived smokers rated END-stimuli as significantly less pleasurable than the corresponding control stimuli ($t(18)=-3.39$, $p=.003$). BEGIN-stimuli were rated as more pleasurable than END-stimuli ($t(18)=2.69$, $p=.015$). Non-smokers rated BEGIN- and END-stimuli significantly less pleasurable than the corresponding control stimuli (BEGIN: $t(16)=-2.49$, $p=.024$; END: $t(16)=-3.21$,

$p=.005$). Comparing both groups, non-deprived smokers rated BEGIN-stimuli as significantly more pleasurable than non-smokers ($t(23.09)=3.57$, $p=.002$).

Arousal (Table 2). Non-deprived smokers rated BEGIN-stimuli as significantly more arousing than the corresponding control stimuli ($t(18)=3.65$, $p=.002$). The same was true for non-smokers ($t(16)=2.17$, $p=.046$). Comparing both groups, no significant differences were observed.

--- insert Table 2 ---

Deprived smokers compared to non-deprived smokers

The ratings of one deprived smoker had to be excluded from the analysis due to excessive missing values.

Craving (Figure 1, Table 2). In deprived smokers, BEGIN- and END-stimuli led to more craving than the corresponding control stimuli (BEGIN: $t(18)=5.96$, $p<.001$; END: $t(18)=4.88$, $p<.001$). BEGIN-stimuli led to higher craving than END-stimuli ($t(18)=4.38$; $p<.001$). In comparison with non-deprived smokers, deprived smokers showed higher craving ratings for BEGIN- and END-stimuli (BEGIN: $t(36)=2.86$, $p=.007$; END: $t(36)=3.71$, $p=.001$).

Valence (Table 2). Deprived smokers rated BEGIN-stimuli as significantly more pleasurable than the corresponding control stimuli ($t(18)=3.07$, $p=.007$) and END-stimuli ($t(18)=2.87$, $p=.010$). In comparison with non-deprived smokers, no significant differences were observed.

Arousal (Table 2). Deprived smokers rated BEGIN- and END-stimuli as significantly more arousing than the corresponding control stimuli (BEGIN: $t(18)=4.34$, $p<.001$; END: $t(18)=4.48$, $p<.001$). BEGIN-stimuli were rated as more arousing than END-stimuli ($t(18)=4.82$, $p<.001$). In comparison with non-deprived smokers, deprived smokers rated BEGIN- as well as END-stimuli as significantly more arousing (BEGIN: $t(36)=5.58$, $p<.001$; END: $t(36)=4.08$, $p<.001$).

Ratings of additional stimuli

Craving (Table 2). “Taking a cigarette out of its box” led to higher craving in non-deprived smokers and deprived smokers than the corresponding control stimuli (non-deprived smokers: $t(18)=4.43$, $p<.001$; deprived smokers: $t(18)=5.99$, $p<.001$). No such differences were found for non-smokers. Similar results were found for “the last puff” (non-deprived smokers: $t(18)=4.00$, $p=.001$; deprived smokers: $t(18)=5.60$, $p<.001$).

Valence (Table 2). Deprived smokers rated “taking a cigarette out of its box” as significantly more pleasurable than the corresponding control stimuli ($t(18)=3.64$, $p=.002$). Non-smokers rated this stimulus as significantly less pleasurable than control stimuli ($t(16)=-2.72$, $p=.015$). No significant results were found for non-deprived smokers. Similar results were found for “the last puff” (deprived smokers: $t(18)=3.54$, $p=.002$; non-smokers: $t(16)=-3.09$, $p=.007$).

Arousal (Table 2). “Taking a cigarette out of its box” was rated significantly more arousing than the corresponding control stimuli by non-deprived smokers and deprived smokers (non-deprived smokers: $t(18)=4.62$, $p<.001$; deprived smokers: $t(18)=4.49$, $p<.001$). No significant results were found for non-smokers. “The last

puff” was rated as significantly more arousing than the corresponding control stimuli by deprived smokers ($t(18)=4.41$, $p<.001$).

Exploratory analyses of differences between the four smoking stimuli

To account for group differences in changes over time, the interaction between *group* and *stage* was analyzed in two 2 x 4 plans.

Craving (Table 2). Comparing non-deprived smokers and non-smokers, significant main effects of *group* and *stage* as well as a significant *group* x *stage* interaction were found (for all F-values $p<.001$). Post hoc analyses revealed that for non-deprived smokers, END-stimuli led to significantly lower craving than all other smoking stimuli (all $p<.01$). BEGIN-stimuli led to significantly more craving than “the last puff” (mean difference = 0.65, $p=.045$), whereas no significant differences were found between BEGIN-stimuli and “taking a cigarette out of its box”.

Comparing deprived smokers and non-deprived smokers, significant main effects of *group* and *stage* were found, with deprived smokers showing higher craving (all $p<.004$). Post hoc analyses in both groups combined revealed that END-stimuli led to significantly lower craving than all other smoking stimuli (all $p<.001$). BEGIN-stimuli led to significantly more craving than “taking a cigarette out of its box” (mean difference = 0.25, $p=.038$) and “the last puff” (mean difference = 0.58, $p=.007$), whereas no significant differences were found between “taking a cigarette out of its box” and “the last puff”.

Valence (Table 2). Comparing non-deprived smokers and non-smokers, main effects of *group* and *stage* were found, with non-deprived smokers showing higher ratings

(all $p < .003$). Post hoc analyses in both groups combined revealed that “taking a cigarette out of its box” was rated as significantly more pleasurable than “the last puff” and END-stimuli. BEGIN-stimuli were rated as significantly more pleasurable than “the last puff” (all $p < .05$).

Comparing deprived smokers and non-deprived smokers, a significant main effect of *stage* was found ($F(1.90, 68.33) = 11.39, p < .001$). Post hoc analyses in both groups combined revealed that END-stimuli were rated as significantly less pleasurable than all other smoking stimuli (all $p < .01$).

Arousal (Table 2). Comparing non-deprived smokers and non-smokers, no significant results were found.

Comparing deprived smokers and non-deprived smokers, significant main effects of *group* and *stage* were found, with deprived smokers showing higher ratings (all $p < .002$). Post hoc analyses in both groups combined revealed that END-stimuli were rated as significantly less arousing than all other smoking stimuli (all $p < .05$).

Brain responses to BEGIN- and END-stimuli

Non-deprived smokers compared to non-smokers

BEGIN

For the contrast BEGIN, non-deprived smokers showed activations in the VTA, the ventral striatum, the OFC, the ACC, the DLPFC, the hippocampus, and the insula (Table 3). In non-smokers we found activations in the OFC, the ACC and in the DLPFC. Comparing both groups, non-deprived smokers exhibited significantly greater activations than non-smokers in the VTA, the DLPFC, and the insula (Table 4).

--- insert Table 3 ---

---insert Table 4---

END

For the contrast END, non-deprived smokers showed deactivations in the ventral striatum, the ACC, the DLPFC, and the insula (Table 3). Yet despite deactivations, they also showed activations in the OFC, the DLPFC, the hippocampus, and the insula. No activations or deactivations were found for non-smokers. Comparing both groups, non-deprived smokers showed stronger activations than non-smokers in the OFC and the DLPFC (Table 4).

Differences between the contrasts BEGIN and END (BEGIN-END).

Non-deprived smokers showed stronger neuronal activity for BEGIN than for END in the ventral striatum and the ACC (Table 5). Non-smokers showed no differences between these contrasts. Comparing both groups, non-deprived smokers revealed smaller differences between BEGIN and END in the OFC than non-smokers (Table 4).

--- insert Table 5 ---

Figure 2 visualises the most important findings. “Lighting up a cigarette”, a prototypical BEGIN-stimulus, led to activations in the ACC, the DLPFC and the ventral striatum of non-deprived smokers. In contrast, “stubbing out a cigarette butt”, a prototypical END-stimulus, triggered deactivations in exactly the same structures.

--- insert Figure 2 ---

Deprived smokers compared to non-deprived smokers

BEGIN

For the contrast BEGIN, deprived smokers showed activations in the VTA, the OFC, the ACC, the DLPFC, the hippocampus, and the insula (Table 3). In comparison with non-deprived smokers, deprived smokers showed a significantly stronger activation in the DLPFC (Table 4). However, at a different voxel-coordinate, non-deprived smokers also showed a significantly stronger activation than deprived smokers in this structure.

END

For the contrast END, deprived smokers showed deactivations in OFC and DLPFC. They also showed activations in the OFC and the ventral striatum (Table 3). In comparison with non-deprived smokers, an effect of deprivation was found in the OFC, the DLPFC, and the insula, with deprived smokers showing significantly lower neuronal activity than non-deprived smokers (Table 4).

Differences between the contrasts BEGIN and END

In deprived smokers, differences between BEGIN and END were found in the VTA, the OFC, the ACC, the DLPFC, and the insula (Table 5). In comparison with non-deprived smokers, deprived smokers revealed significantly greater differences in the OFC and the DLPFC (Table 4).

Brain responses to additional smoking stimuli (TAKING OUT, LAST PUFF).

For the contrast TAKING OUT, non-deprived smokers showed activations in the OFC, the ACC, the DLPFC, and the insula (Table 3). Additionally, they showed deactivations in the ventral striatum, the ACC, and the DLPFC. Deprived smokers showed activations in the OFC, the ACC, the DLPFC, the hippocampus, and the insula (Table 3). No activations or deactivations were found for non-smokers.

For the contrast LAST PUFF, non-deprived smokers showed activations in the VTA, the ventral striatum, the OFC, the ACC, the DLPFC, the amygdala, the hippocampus, and the insula (Table 3). Deprived smokers showed activations in the ventral striatum, the OFC, the ACC, the DLPFC, the amygdala, the hippocampus, and the insula (Table 3). No activations or deactivations were found for non-smokers.

Exploratory analysis of differences between the four smoking stimuli

To account for group differences in changes over time, the interaction between *group* and *stage* was analyzed in two 2 x 4 plans.

Comparing non-deprived smokers and non-smokers, a significant interaction was found in the right amygdala (Table 6); the greatest differences between both groups appeared for BEGIN and LAST PUFF. Non-deprived smokers showed strong amygdala activations for LAST PUFF and deactivations for BEGIN; the reverse was true for non-smokers. Contrast values for TAKING out and END were close to zero in both groups.

Comparing deprived smokers and non-deprived smokers, a significant main effect of *stage* was found in the OFC, the ACC, and the insula. Figure 3 shows the contrast estimates for the combined group (non-deprived and deprived smokers) and the four conditions for the ACC. Notably, contrast values decreased over the time course of the smoking-ritual and showed deactivations for END. Similar progressions were found for the OFC and the insula.

--- insert Table 6 ---

--- insert Figure 3 ---

Additionally to this main effect, we found significant interactions between *group* and *stage* in the DLPFC and the hippocampus (Table 6). Figure 4 shows the DLPFC-contrast estimates for both groups in the four conditions. In the DLPFC, deprived smokers showed a decrease in contrast estimates over the four conditions resulting in deactivations for LAST PUFF and END. Non-deprived smokers showed an increase in contrast estimates up to the point of LAST PUFF (deactivations for TAKING OUT and BEGIN) and deactivations for END. Notably, for END, deprived smokers showed a stronger deactivation than non-deprived smokers. Opposing trends in both groups can be observed for TAKING OUT and LAST PUFF. The greatest difference between the groups appeared for TAKING OUT and only a small

difference can be seen for BEGIN. Responses in the hippocampus showed a less regular progression. For deprived smokers, activations were found for TAKING OUT and LAST PUFF, whereas deactivations were found for BEGIN and END. In non-deprived smokers, deactivations occurred for TAKING OUT, whereas there were activations in response to the other conditions. The greatest differences between non-deprived smokers and deprived smokers appeared for TAKING OUT and END.

--- insert Figure 4 ---

Discussion

This study addressed two main questions: firstly, we wanted to explore whether stimuli associated with the beginning of smoking (BEGIN-stimuli) and stimuli associated with the terminal stage of smoking (END-stimuli) differentially activate the neural addiction network of smokers. This was based on the hypothesis that the reactivity evoked by a drug-associated stimulus is critically influenced by its position in the drug-consumption ritual. Specifically, we expected BEGIN-stimuli to be excitatory as reflected in activations of the addiction network whereas END-stimuli should have no excitatory or even inhibitory effects as reflected in deactivations. Secondly, we were interested in the effects of deprivation on these processes and expected an enhancement of differential effects of BEGIN- and END-stimuli under deprivation. Additional exploratory questions addressed the issue whether other stimuli from the smoking ritual also evoke differential responses.

Craving, valence and arousal

Generally, the used stimuli were rated in accordance with our hypotheses.

All smoking stimuli elicited higher craving than the corresponding control stimuli in non-deprived and deprived smokers. Furthermore and in line with our previous findings (Mucha *et al*, 1999, 2008), in both groups BEGIN-stimuli elicited more craving than END-stimuli. Interestingly, stimuli depicting events immediately before the termination of smoking (“the last puff”) also evoked more craving than END-stimuli even though they show a similar association with the peak of the nicotine-effect. In contrast, stimuli depicting events immediately before the start of actual

smoke-consumption (“taking a cigarette out of its box”) elicited less craving than BEGIN-stimuli. Overall, deprived smokers reported more craving in response to smoking stimuli than non-deprived smokers; this pattern also emerged in response to control stimuli, most probably due to craving baseline differences (see QSU pre-scan scores). Differences between the craving ratings elicited by smoking vs. control stimuli were similar for non-deprived and deprived smokers. Thus, considering craving, we conclude that stimuli associated with different stages of the smoking ritual differentially affect craving in smokers. These effects are only slightly affected by deprivation.

A difference between BEGIN- and END-stimuli was also found for valence: similar to Mucha and colleagues (1999, 2008), non-deprived and deprived smokers rated BEGIN-stimuli as more pleasurable than END-stimuli. At least for deprived smokers, this difference also occurred for arousal ratings. These results demonstrate that differences between BEGIN- and END-stimuli do not only exist for craving, but also for two important dimensions of emotional experience. For deprived smokers we found that they were significantly more aroused by smoking stimuli than non-deprived smokers. This observation supports the assumption of an enhancement of the incentive value of smoking stimuli under deprivation (Stewart *et al*, 1984, Toates, 1994; Berridge, 2004). In sum, we conclude that BEGIN- and END-stimuli lead to pronounced differences in ratings and therefore should also differentially activate the neural addiction network.

Neural impact of BEGIN- and END-stimuli in non-deprived smokers

In non-deprived smokers, prototypical BEGIN-stimuli (“lighting a cigarette”) triggered activations in almost the entire addiction-network. Significant stronger activations

than in non-smokers were found in the VTA, the DLPFC, and the insula, three structures critically involved in reward processing, the generation and maintenance of consumption related goals, and craving (Everitt and Robbins, 2005; Wilson *et al*, 2004; Naqvi and Bechara, 2009). This is in accordance with our hypothesis and resembles results obtained by others (e.g. Due *et al*, 2002; Brody *et al*, 2002). In contrast, prototypical END-stimuli (“stubbing out a cigarette butt”) led to a more complex pattern of activations and deactivations. Importantly, in non-deprived smokers, deactivations in response to END-stimuli were found in parts of the reward- and the control-sub-circuit: ventral striatum and ACC. Contrasting BEGIN- and END-stimuli, we also found higher neural activity towards BEGIN-stimuli in these two structures. This shows that END-stimuli have indeed a differential impact on the neuronal activity in the addiction-network of non-deprived smokers. Since the ventral striatum and the ACC play important roles for addiction in terms of incentive motivation, reward detection, and disinhibition (e.g. Lubman *et al*, 2004; Robinson and Berridge, 1993, 2003; Volkow *et al*, 2003, 2004), the observed deactivations in these structures may indicate inhibitory effects of prototypical END-stimuli.

The role of the ventral striatum in reward processing and reward expectancy is widely acknowledged (e.g., Spanagel and Weiss, 1999; Wise, 2004) and its activity has been shown to be correlated with the magnitude of a received reward (Knutson *et al*, 2001, 2005). Moreover, unexpected omissions of a reward as well as stimuli predictive of reward omissions (i.e. a conditioned inhibitor) lead to an inhibition of dopaminergic neurons (Schultz, 1998, 2002; Tobler *et al*, 2003). Furthermore, previous behavioral studies demonstrated that stimuli predicting the absence of drug can suppress drug-seeking (Kearns *et al* 2005). Therefore, the deactivations observed in our study might point to a reduction of an incentive motivational state in response to prototypical END-stimuli in smokers.

The ACC is part of the limbic affect-response system (Wexler *et al*, 2001) and interconnected with the ventral striatum (Vogt *et al*, 1992; Devinsky *et al*, 1995; Bush *et al*, 2000). In addicts, it is one of the structures, in which activity in response to stimuli paired with a variety of drugs such as nicotine (Brody *et al*, 2002; Due *et al*, 2002; McBride *et al*, 2006; McClernon *et al*, 2005), cocaine (Maas *et al*, 1998; Garavan *et al*, 2000; Kilts *et al*, 2001; Childress *et al*, 1999; Wexler *et al*, 2001) and heroin (Daglish *et al*, 2001) is most frequently reported. Moreover, its importance for addiction is emphasized by the fact that surgical lesioning of the ACC can decrease drug consumption in addicts (Sharma, 1974; Kanaka and Balasubramaniam, 1978). Likewise, smokers treated with bupropion showed an attenuation of both, cue-induced cigarette craving and ACC activation (Brody *et al*, 2004). Like the ventral striatum, the ACC is involved in reward processing and it also seems to be sensitive to the magnitude of a received reward (Shidara *et al*, 2002; Peoples, 2002; Bush *et al*, 2002; Kirsch *et al*, 2003). It has also been shown to play a role in anticipation (Murtha *et al*, 1996). In conditioning studies, the ACC was found to discriminate between a reinforced CS (CS+) and a non-reinforced CS (CS-) (Martin-Soelch *et al*, 2007). Therefore, the differential activation of the ACC by BEGIN- and END-stimuli could be due to different anticipatory states, resulting from the discrimination of stimuli with different predictive values. Finally, the ACC plays a role in the detection of conflicts (Braver *et al*, 2001) and thus is activated in tasks that generate conflicting response tendencies (e.g. Carter *et al*, 1999). As Wexler (2001) notes, subjects in cue-reactivity paradigms may be faced with an internal response conflict and the need to inhibit certain response tendencies. This also could contribute to our data, with very pronounced conflicts in response to BEGIN-stimuli but not in response to END-stimuli.

Surprisingly, although these differences between BEGIN- and END-stimuli were significant in non-deprived smokers but not in non-smokers, there were no significant differences between both groups. This could possibly be due to a motivational impact of smoking-stimuli on non-smokers. For example, BEGIN-stimuli could be aversive because they are associated with smoke; END-stimuli might have a relieving effect. The ventral striatum and the ACC are known to be involved in a wide range of positive as well as negative emotional processes (Rolls, 1999; Martin-Soelch, 2007). Thus, although stimuli can have different motivational impacts, they can lead to activations in the same brain structures.

Neural impact of BEGIN- and END-stimuli in deprived smokers

The comparison between deprived smokers and non-deprived smokers revealed some interesting results. Regarding BEGIN-stimuli ("lighting a cigarette"), we expected that deprived smokers would show enhanced neuronal activity compared to non-deprived smokers. However, both groups barely differed (see also Geier *et al*, 2000 and Mueller *et al*, 1998 for similar results regarding the modulation of the startle-response). Regarding END-stimuli ("stubbing out a cigarette butt"), we also expected enhanced effects under deprivation, i.e. lower responses in deprived smokers compared to non-deprived smokers. Indeed, we observed lower responses in OFC, DLPFC, and insula in deprived smokers compared to non-deprived smokers. Moreover, we found deactivations as well as activations in the OFC and exclusive deactivations in the DLPFC of deprived smokers. These structures are associated with craving, drug-expectancy, and planning of drug consumption (Goldstein and Volkow, 2002; Wilson *et al*, 2004; Naqvi and Bechara, 2009). A review regarding the role of drug-expectancy on neuronal responses to drug-cues (Wilson *et al*, 2004)

found that only active drug-users showed OFC and DLPFC activations in response to cues. Drug-users in treatment, who are supposed to have no expectancy of their drug in response to cues, showed no such activations. This was further confirmed by McBride *et al* (2006) who explicitly manipulated the expectancy to smoke after a cue exposure experiment. Similar effects could account for our data. One essential feature of END-stimuli may be that the perceived availability of smoke is reduced (Mucha *et al*, 2008). This could lead to a lower drug- expectancy and less planning of drug-consumption, especially in deprived smokers. Overall, deprivation particularly seems to affect the responses to END-stimuli, whereas responses to BEGIN-stimuli seem to be only slightly affected. As a consequence, we found significantly greater differences between BEGIN- and END-stimuli in deprived smokers than in non-deprived smokers in OFC and DLPFC.

Thus, deprivation does not simply enhance responses to all drug stimuli. Rather, the effect of deprivation strongly depends on the stage of the consumption ritual a smoking stimulus is associated with.

Neural impact of additional stimuli

Two additional stimuli were included in our study, “taking a cigarette out of its box” and “the last puff”. In non-deprived smokers, “taking a cigarette out of its box” led to a complex pattern of activations and deactivations. Activations as well as deactivations occurred in the reward- and control-sub-circuits (ventral striatum, ACC, DLPFC). “The last puff” led to activations in the entire network. Surprisingly, although “the last puff” directly precedes the prototypical END-stimuli, neural responses are more similar to those of prototypical BEGIN-stimuli. Likewise, “taking a cigarette out of its box”

directly precedes prototypical BEGIN-stimuli, but the results are more similar to those of prototypical END-stimuli.

Comparing non-deprived smokers and non-smokers (*group x stage* analysis), we found stronger amygdala activation to “the last puff” in non-deprived smokers and to BEGIN-stimuli in non-smokers. Amongst other functions, the amygdala is involved in the facilitation of attention to salient events and processes stimuli predictive of aversive as well as positive events (Phelps and LeDoux, 2005; LeDoux, 2000; Baxter and Murray, 2002). In addiction research amygdala activity is related to the processing of discrete cues (e.g. Everitt and Robbins, 2005). The activation in non-smokers emphasizes the motivational significance of BEGIN-stimuli in this group as mentioned before. The activation in non-deprived smokers suggests “the last puff” to be a very salient stimulus for this group. This might be explained by the fact that it displays *acute* smoke availability and intake. Also, nicotine intake might be higher with “the last puff” due to the reduced air resistance of a cigarette butt. “Taking a cigarette out of its box” and BEGIN-stimuli predict a rather *prospective* nicotine availability. In a non-deprived state, this may not be as salient as “the last puff”.

In the *group x stage* analysis for deprived smokers and non-deprived smokers, a significant main effect for the factor *stage* occurred in the ACC, the OFC and the insula. OFC- and ACC-responses diminished over the time course of smoking, leading to pronounced deactivations in response to END-stimuli. The role of the ACC in addiction was discussed above. The OFC is linked to similar functions, particular to craving and to the expectation of drug (Goldstein and Volkow, 2002). This again shows that END-stimuli seem to yield a unique response in the addiction network that is different from prototypical BEGIN-stimuli and other stimuli of the smoking ritual. In this analysis, deactivations to END-stimuli have also been found in the insula. The

role of the insula in addiction has only recently been emphasised (Naqvi and Bechara, 2009) and like the OFC it has become linked to craving. However, the OFC seems to be more involved in the cognitive aspects of craving like drug expectation (Goldstein and Volkow, 2002; London *et al*, 2000; see also Cardinal *et al*, 2002). The insula, due to its function in monitoring physiological processes (Craig, 2009; Naqvi and Bechara, 2009), seems to be more involved in the bodily aspects. Furthermore, significant interactions in the DLPFC and the hippocampus show a remarkably difference between deprived and non-deprived smokers. As mentioned above, the DLPFC is crucially involved in the generation and maintenance of consume related goals. Its activity is thereby modulated by the perceived availability to consume the drug (Wilson *et al.*, 2004). In deprived smokers, neuronal activity in the DLPFC is highest in response to “taking a cigarette out of its box” and diminishes over time. “The last puff” and END-stimuli are accompanied with deactivations of DLPFC activity. We therefore conclude that in a deprived state the most salient smoking stimuli are those that predict more *prospective* drug availability. As noted above, in a non-deprived, i.e. satiated state, stimuli predicting rather *acute* drug availability seem to be the most salient cues. This can also be seen in the DLPFC activity of non-deprived smokers that is deactivated in response to “taking a cigarette out of its box”, BEGIN-stimuli, and END-stimuli. Only “the last puff” leads to strong DLPFC activations in this group. It is well known that drug availability plays an important role in the modulation of cue-reactivity (Wertz and Sayette, 2001; Carter and Tiffany, 2001; Wilson *et al*, 2004, McBride *et al*, 2006). Furthermore, Mucha *et al* (2008) suggested that the perceived smoke availability is an important factor for the differential reactivity to BEGIN- and END-stimuli. Thus, on a neural level, our results seem to confirm their findings but also lead to a possible extension: in non-deprived smokers particularly stimuli depicting the *acute* availability of smoke lead to

activations in the addiction network. In contrast, in a deprived state mainly stimuli predicting a prospective availability lead to the strongest activations. Similar effects were found in a study on food deprivation (Siep *et al*, 2009); subjects saw pictures of high or low calorie food while being either hungry or satiated. The results revealed an increased reward processing in response to low calorie food in satiated subjects but in response to high calorie food in deprived subjects.

Previous findings regarding the effects of drug deprivation on subjective (Gross *et al*, 1993; Waters and Feyerabend, 2000; Mucha *et al*, 1999), physiological (Geier *et al*, 2000), and neuronal responses are mixed. For neuronal activity, deprived smokers (compared to non-deprived smokers) have been found to show weaker (David *et al*, 2007), equal (McBride *et al*, 2006; McClernon *et al*, 2005) or greater activity (McClernon *et al*, 2008) in response to smoking cues. Yet, these studies did not differentiate their stimuli regarding to the position in the smoking ritual and the perceived *acute* or *prospective* drug availability. This might be one factor that can explain differences between studies. We have however to note that these brain data are not fully in accordance with subjective data. For example, both, non-deprived smokers and deprived smokers gave higher craving ratings in response to BEGIN-stimuli than in response to the other smoking stimuli.

Limitations

This study was the first investigation of neuronal responses to stimuli related to different stages of the smoking-ritual. Careful attention was paid to the development of the stimulus and control material and the composition of three participant groups: non-smokers, non-deprived smokers and deprived smokers. However, some limitations may lie in possible habituation effects developing over the experimental course. Further, an unwanted transfer effect due to the random arrangement of the

different stages of the smoking ritual, which normally has a strictly determined sequence, might have occurred. Eventually, we were able to show some deprivation effects, yet more pronounced effects might have been observed with a longer deprivation-period.

Conclusions

Our results support the notion that stimuli depicting the terminal stage of the smoking-ritual (END-stimuli) modulate neuronal activity in the addiction network of smokers in a different way than stimuli depicting the beginning of the smoking ritual (BEGIN-stimuli). BEGIN-stimuli lead to significantly stronger activations than END-stimuli and, furthermore, END-stimuli lead to partial deactivations in the network. As expected, deprivation leads to a stronger differentiation between BEGIN- and END-stimuli in deprived than in non-deprived smokers. Furthermore, activity in response to END-stimuli is significantly lower in deprived smokers, whereas responses to BEGIN-stimuli differ only marginally. Deprived smokers seem to respond particularly strong to stimuli signalling *prospective* drug availability, whereas non-deprived smokers respond particularly strong to stimuli signalling *acute* drug availability.

Disclosure/Conflict of Interest

Ronald F. Mucha has invested in a marketing venture to use pictures of the end of smoking for symbolizing smoking with little craving. This could be perceived as a conflict of interest, although the present study was conceived and carried out independent of this.

All other authors do not have any conflicts of interest, financial or otherwise, that might bias this work.

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Table 1. Mean (SE) of age, years smoked, cigarettes/day in the last 12 months, scores on the Fagerström Test of Nicotine Dependence (FTND), the Questionnaire of Smoking Urges (QSU), and carbon monoxide (CO)-measures. Groups with same indices did not differ significantly.

	NON-SMOKERS (n=17; 9f)	NON-DEPRIVED SMOKERS (n=19; 11f)	DEPRIVED SMOKERS (n=20; 10f)
Age (years)	24.59 ^a (0.79)	27.21 ^a (1.37)	25.80 ^a (1.68)
Years smoked	--	10.77 ^a (1.17)	10.29 ^a (1.75)
Cigarettes/day	--	20.79 ^a (0.83)	19.43 ^a (1.33)
FTND	--	4.58 ^a (0.49)	3.95 ^a (0.39)
QSU-Baseline	1.11 ^a (0.03)	2.44 ^b (0.19)	2.82 ^b (0.20)
QSU-pre scan	1.07 ^a (0.35)	2.34 ^b (0.20)	4.78 ^c (0.24)
CO-Baseline	2.59 ^a (0.23)	28.32 ^b (2.69)	28.25 ^b (2.68)
CO-pre scan	2.59 ^a (0.24)	28.53 ^b (2.56)	6.60 ^c (0.56)

Table 2. Mean (SE) of craving, valence and arousal ratings (range for all three scales: 1-9) for smoking (S1, S2, S3, S4) and control stimuli (T1, T2, T3, T4) for non-smokers, non-deprived smokers, and deprived smokers. S2 and S4 (respectively T2 and T4) are highlighted because we mainly focus on BEGIN- (S2) and END- (S4) stimuli.

	SMOKING STIMULI				CONTROL STIMULI			
	S1	S2	S3	S4	T1	T2	T3	T4
NON-SMOKERS								
Craving	1.00 (.00)	1.00 (.00)	1.00 (.00)	1.00 (.00)	1.00 (.00)	1.00 (.00)	1.00 (.00)	1.00 (.00)
Valence	4.40 (.40)	4.22 (.45)	4.03 (.45)	4.06 (.46)	5.92 (.29)	5.64 (.31)	5.70 (.33)	5.87 (.28)
Arousal	2.83 (.32)	2.97 (.33)	3.04 (.38)	3.10 (.36)	2.34 (.29)	2.50 (.30)	2.59 (.33)	2.45 (.27)
NON-DEPRIVED SMOKERS								
Craving	4.57 (.52)	4.70 (.53)	4.05 (.42)	3.31 (.35)	2.32 (.32)	2.40 (.35)	2.35 (.34)	2.36 (.32)
Valence	6.06 (.20)	6.00 (.22)	5.50 (.25)	5.08 (.32)	5.91 (.22)	5.72 (.30)	5.73 (.28)	5.98 (.25)
Arousal	3.77 (.33)	3.85 (.35)	3.71 (.30)	3.44 (.32)	3.09 (.32)	3.11 (.31)	3.40 (.36)	3.05 (.31)
DEPRIVED SMOKERS								
Craving	6.30 (.42)	6.66 (.44)	6.16 (.49)	5.52 (.48)	3.64 (.46)	3.50 (.46)	3.60 (.46)	3.57 (.46)
Valence	5.39 (.21)	5.69 (.35)	5.54 (.28)	4.64 (.20)	4.80 (.16)	4.51 (.23)	4.29 (.25)	4.77 (.18)
Arousal	6.01 (.27)	6.25 (.25)	5.87 (.28)	5.18 (.28)	4.10 (.37)	4.27 (.38)	4.14 (.40)	3.90 (.32)

Table 3. Significant activations and deactivations for the contrasts TAKING OUT, BEGIN, LAST PUFF and END in non-smokers, non-deprived smokers and deprived smokers.

Contrast	Structures	Side	x	y	z	t_{\max} score	Cluster size	p_{corr}
NON-SMOKERS								
TAKING OUT	No significant results							
BEGIN								
<i>activations</i>	Orbitofrontal cortex	L	0	54	-15	4.29	292	.009
	Orbitofrontal cortex	R	3	54	-18	4.22	180	.011
	Anterior cingulate cortex	R	6	45	27	3.47	138	.034
	Dorsolateral prefrontal cortex	R	18	45	36	4.29	54	.015
<i>deactivations</i>	No significant results							
LAST PUFF	No significant results							
END	No significant results							
NON-DEPRIVED SMOKERS								
TAKING OUT								
<i>activations</i>	Orbitofrontal cortex	L	-42	18	-9	5.40	240	<.001
	Anterior cingulate cortex	L	3	21	21	3.69	248	.020
	Anterior cingulate cortex	R	6	18	24	3.82	44	.012
	Dorsolateral prefrontal cortex	L	-33	3	54	5.90	450	<.001
	Dorsolateral prefrontal cortex	R	27	0	57	4.64	198	.004
	Insular cortex	L	-39	15	-6	6.43	259	<.001
	Insular cortex	R	33	24	3	4.88	137	<.001
<i>deactivations</i>	Ventral striatum	R	18	9	-12	3.25	56	.025
	Anterior cingulate cortex	R	12	36	12	3.95	80	.008
	Dorsolateral prefrontal cortex	R	36	-12	69	4.56	14	.006
BEGIN								
<i>activations</i>	Ventral tegmental area		0	-15	-9	3.39	26	.001
	Ventral striatum	L	-12	12	-6	3.15	35	.029
	Orbitofrontal cortex	L	-6	45	-6	4.98	393	.001
	Orbitofrontal cortex	R	30	24	-24	4.18	453	.013
	Anterior cingulate cortex	L	3	24	24	5.35	365	<.001
	Anterior cingulate cortex	R	3	24	27	5.34	214	<.001
	Dorsolateral prefrontal cortex	L	-18	60	3	4.73	811	.003
	Dorsolateral prefrontal cortex	R	33	-3	54	5.11	189	.001
	Hippocampus	L	-24	-27	-18	3.69	203	.025
	Insular cortex	L	-33	21	3	5.18	169	<.001
	Insular cortex	R	30	24	-21	4.16	18	.005
<i>deactivations</i>	No significant results							
LAST PUFF								
<i>activations</i>	Ventral tegmental area		3	-18	-15	4.60	26	<.001
	Ventral striatum	L	-15	6	-12	3.64	22	.007

Ventral striatum	R	15	9	0	3.38	91	.017
Orbitofrontal cortex	L	-42	36	-6	7.20	833	<.001
Orbitofrontal cortex	R	36	30	-15	5.15	861	<.001
Anterior cingulate cortex	L	-6	30	30	6.61	332	<.001
Anterior cingulate cortex	R	3	18	27	4.86	177	<.001
Dorsolateral prefrontal cortex	L	-42	48	24	6.79	2017	<.001
Dorsolateral prefrontal cortex	R	42	18	39	6.26	2231	<.001
Amygdala	L	-30	0	-27	5.85	69	<.001
Amygdala	R	36	0	-24	5.34	80	<.001
Hippocampus	L	-24	-27	-21	5.33	465	<.001
Hippocampus	R	33	-15	-12	6.17	495	<.001
Insular cortex	L	-30	21	-9	6.09	513	<.001
Insular cortex	R	39	0	6	5.47	421	<.001

deactivations

No significant results

END

activations

Orbitofrontal cortex	L	-21	30	-12	6.72	393	<.001
Orbitofrontal cortex	R	24	36	-15	4.05	148	.020
Dorsolateral prefrontal cortex	L	-39	9	33	4.39	56	.010
Dorsolateral prefrontal cortex	R	51	42	9	4.71	196	.003
Hippocampus	L	-30	-39	-15	4.53	70	.002
Insular cortex	L	-36	9	-15	4.03	142	.009

deactivations

Ventral striatum	R	9	3	-9	3.97	16	.003
Anterior cingulate cortex	L	3	39	15	4.19	96	.004
Anterior cingulate cortex	R	15	36	12	5.20	159	<.001
Dorsolateral prefrontal cortex	R	18	57	3	4.07	52	.032
Insular cortex	R	42	-12	12	3.77	59	.019

DEPRIVED SMOKERS

TAKING OUT

activations

Orbitofrontal cortex	L	-12	51	-3	5.15	680	<.001
Orbitofrontal cortex	R	24	36	-24	4.43	429	.005
Anterior cingulate cortex	L	-9	51	0	5.57	306	<.001
Anterior cingulate cortex	R	3	36	0	4.48	84	.001
Dorsolateral prefrontal cortex	L	-15	54	6	5.38	859	<.001
Dorsolateral prefrontal cortex	R	33	-12	63	4.17	260	.023
Hippocampus	L	-12	-39	6	4.99	152	<.001
Hippocampus	R	15	-36	6	4.26	316	.004
Insular cortex	L	-45	6	0	5.61	303	<.001
Insular cortex	R	48	9	-3	4.54	367	.001

deactivations

No significant results

BEGIN

activations

Ventral tegmental area		3	-18	-21	3.66	16	.002
Orbitofrontal cortex	L	-12	48	-6	4.13	532	.014
Anterior cingulate cortex	L	-9	48	-3	3.68	113	.021
Dorsolateral prefrontal cortex	L	-21	-3	66	4.31	1015	.013
Dorsolateral prefrontal cortex	R	36	-9	57	4.43	197	.009
Hippocampus	L	-30	-21	-27	3.92	151	.012
Hippocampus	R	18	-3	-27	3.79	25	.020
Insular cortex	L	-39	3	9	3.73	158	.022

deactivations

No significant results

LAST PUFF
activations

Ventral striatum	L	-3	12	-6	3.12	77	.031
Ventral striatum	R	6	3	-9	3.26	63	.024
Orbitofrontal cortex	L	-36	42	-9	3.91	227	.029
Anterior cingulate cortex	L	-6	48	6	3.54	207	.030
Dorsolateral prefrontal cortex	L	-42	48	6	4.29	755	.014
Dorsolateral prefrontal cortex	R	39	45	3	4.48	354	.008
Amygdala	R	24	-9	-15	3.02	41	.029
Hippocampus	L	-18	-6	-33	3.71	211	.023
Hippocampus	R	21	-6	-33	4.01	287	.010
Insular cortex	L	-42	3	9	4.12	305	.006
Insular cortex	R	39	0	3	4.02	191	.009

deactivations

No significant results

END
activations

Orbitofrontal cortex	L	-9	18	-15	3.80	235	.041
Orbitofrontal cortex	R	3	27	-21	3.97	81	.026
Ventral striatum	L	-3	12	-18	4.24	25	.001

deactivations

Orbitofrontal cortex	R	27	54	-3	4.14	125	.015
Dorsolateral prefrontal cortex	L	-18	6	66	3.91	206	.049
Dorsolateral prefrontal cortex	R	24	51	0	4.58	648	.005

Table 4. Group differences for the contrasts BEGIN, END, and BEGIN-END. Non-deprived smokers were compared to non-smokers; deprived smokers were compared to non-deprived smokers.

Contrast	Structures	Side	x	y	z	t_{\max} score	Cluster size	p_{corr}
NON-DEPRIVED SMOKERS - NON-SMOKERS								
BEGIN	Ventral tegmental area		0	-18	-6	2.74	11	.024
	Dorsolateral prefrontal cortex	L	-39	48	18	3.95	205	.043
	Insular cortex	L	-36	6	-6	3.61	135	.033
END	Orbitofrontal cortex	L	-18	45	-12	4.86	283	.001
	Dorsolateral prefrontal cortex	L	-24	-6	60	4.28	242	.014
	Dorsolateral prefrontal cortex	R	27	6	45	5.43	629	<.001
BEGIN-END	No significant results							
NON-SMOKERS - NON-DEPRIVED SMOKERS								
BEGIN	No significant results							
END	No significant results							
BEGIN-END	Orbitofrontal cortex	L	-21	48	-15	3.84	144	.036
DEPRIVED SMOKERS - NON-DEPRIVED SMOKERS								
BEGIN	Dorsolateral prefrontal cortex	L	-21	30	60	4.46	591	.008
END	No significant results							
BEGIN-END	Orbitofrontal cortex	L	-18	48	-12	3.80	144	.041
	Dorsolateral prefrontal cortex	L	-21	-3	66	4.08	445	.029
NON-DEPRIVED SMOKERS - DEPRIVED SMOKERS								
BEGIN	Dorsolateral prefrontal cortex	L	-18	48	21	4.02	290	.035
END	Orbitofrontal cortex	L	-18	48	-12	4.28	306	.009
	Orbitofrontal cortex	R	27	39	-12	3.80	71	.043
	Dorsolateral prefrontal cortex	L	-24	-3	63	4.19	582	.020
	Dorsolateral prefrontal cortex	R	18	3	66	4.12	795	.027
	Insular cortex	L	-30	21	12	3.54	103	.039
BEGIN-END	No significant results							

Table 5. Comparison of the contrasts BEGIN and END in non-smokers, non-deprived smokers and deprived smokers.

Contrast	Structures	Side	x	y	z	t_{\max} score	Cluster size	p_{corr}
NON-SMOKERS								
BEGIN-END	No significant results							
END-BEGIN	No significant results							
NON-DEPRIVED SMOKERS								
BEGIN-END	Ventral striatum	R	9	3	-6	3.18	18	.029
	Anterior cingulate cortex	L	-6	27	18	3.54	253	.031
	Anterior cingulate cortex	R	12	39	9	3.43	232	.037
END-BEGIN	No significant results							
DEPRIVED SMOKERS								
BEGIN-END	Ventral tegmental area		3	-18	-21	3.10	11	.009
	Orbitofrontal cortex	L	-12	48	-6	4.27	180	.009
	Anterior cingulate cortex	L	-9	48	-3	3.54	67	.031
	Dorsolateral prefrontal cortex	L	-21	3	66	4.88	785	.002
	Dorsolateral prefrontal cortex	R	36	-6	63	3.99	923	.040
	Insular cortex	L	-36	-3	12	3.58	141	.035
END-BEGIN	No significant results							

Table 6. Explorative analysis regarding differences between the contrasts TAKING OUT, BEGIN, LAST PUFF and END. Two 2 x 4 analyses were performed, comparing non-deprived smokers with non-smokers and deprived smokers with non-deprived smokers.

Effect	Structures	Side	x	y	z	F_{\max} score	Cluster size	p_{corr}
NON-DEPRIVED SMOKERS vs. NON-SMOKERS								
Main effects <i>group</i>	No significant results							
<i>stage</i>	No significant results							
Interaction <i>group x stage</i>	Amygdala	R	33	3	-27	5.46	9	.035
NON-DEPRIVED SMOKERS vs. DEPRIVED SMOKERS								
Main effects <i>group</i>	No significant results							
<i>stage</i>	Orbitofrontal cortex	L	-12	51	-3	8.12	92	.028
	Anterior cingulate cortex	L	-6	54	0	7.96	214	.011
	Insular cortex	R	39	-3	3	7.29	318	.028
Interaction <i>group x stage</i>	Dorsolateral prefrontal cortex	R	36	-12	69	8.16	99	.048
	Hippocampus	R	21	-24	-12	7.89	72	.016

Titles and legends to figures

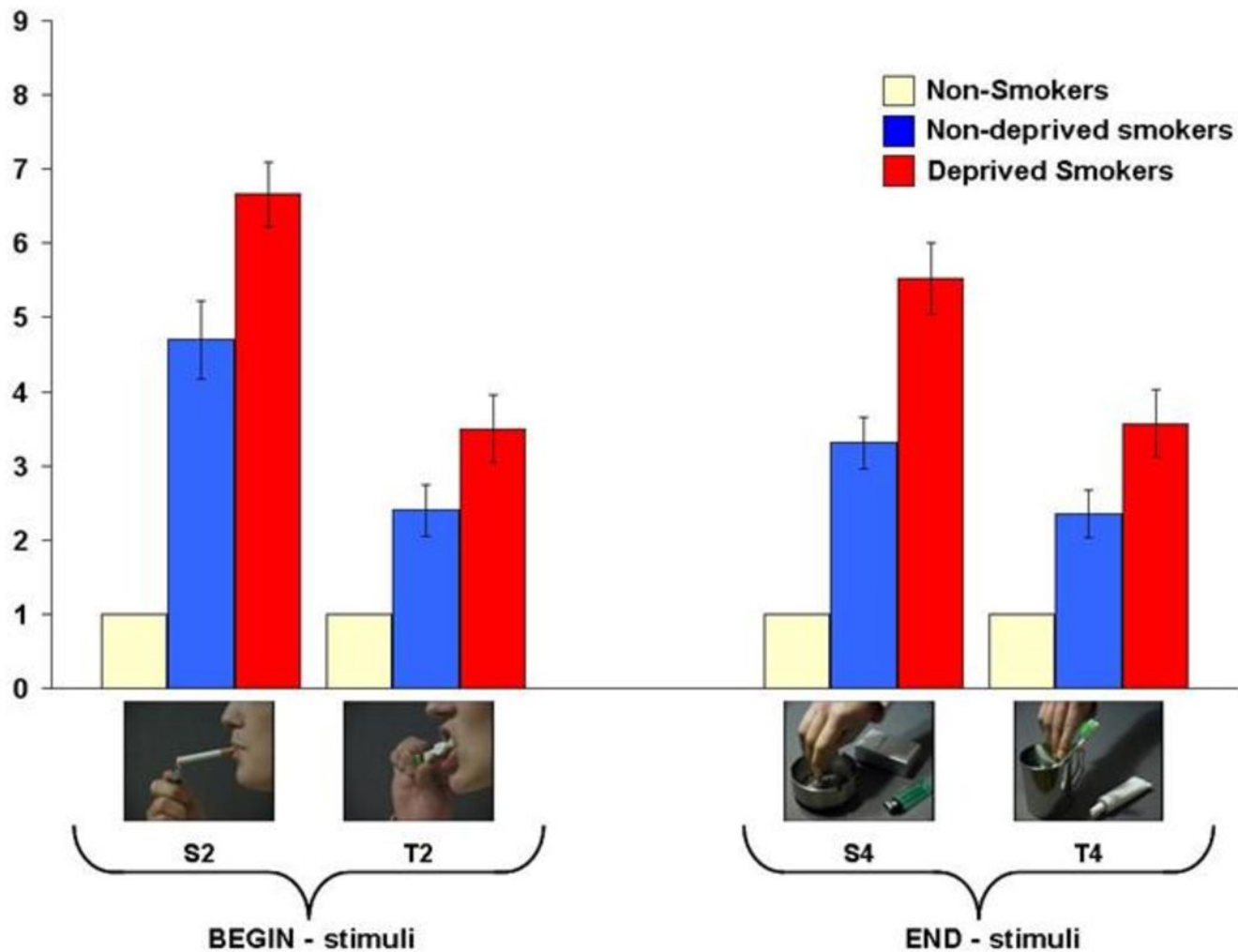
Figure 1. Craving ratings [scale-range: 1-9] for BEGIN- and END-stimuli.

Figure 2. Neural activation and deactivation patterns for BEGIN and END in non-deprived smokers.

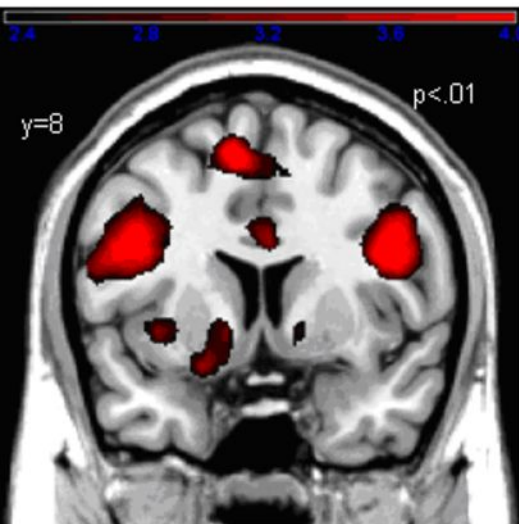
Figure 3. Main effect of *stage* in the ACC for non-deprived smokers and deprived smokers combined.

Figure 4. *Group x stage* interaction in the DLPFC for deprived smokers and non-deprived smokers.

Craving (Range: 1-9)

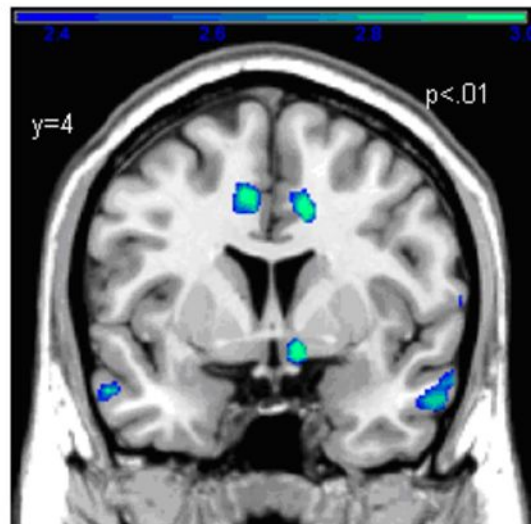


Activations



BEGIN

Deactivations



END

Contrast estimates

