Where There is Smoke There is Fear—Impaired Contextual Inhibition of Conditioned Fear in Smokers

Jan Haaker^{*,1,2}, Tina B Lonsdorf², Dirk Schümann², Nico Bunzeck^{2,3}, Jan Peters^{2,4}, Tobias Sommer² and Raffael Kalisch^{2,5,6}

¹Division of Psychology, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; ²Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; ³Department of Psychology, University of Lübeck, Germany; ⁴Department of Psychology, Biological Psychology, University of Cologne, Cologne, Germany; ⁵Neuroimaging Center (NIC), Focus Program Translational Neuroscience (FTN), Johannes Gutenberg University Medical Center, Mainz, Germany; ⁶Deutsches Resilienz-Zentrum (DRZ), Johannes Gutenberg University Medical Center, Mainz, Germany

The odds-ratio of smoking is elevated in populations with neuropsychiatric diseases, in particular in the highly prevalent diagnoses of post-traumatic stress and anxiety disorders. Yet, the association between smoking and a key dimensional phenotype of these disorders—maladaptive deficits in fear learning and fear inhibition—is unclear. We therefore investigated acquisition and memory of fear and fear inhibition in healthy smoking and non-smoking participants ($N = 349$, 22% smokers). We employed a well validated paradigm of context-dependent fear and safety learning (day 1) including a memory retrieval on day 2. During fear learning, a geometrical shape was associated with an aversive electrical stimulation (classical fear conditioning, in danger context) and fear responses were extinguished within another context (extinction learning, in safe context). On day 2, the conditioned stimuli were presented again in both contexts, without any aversive stimulation. Autonomic physiological measurements of skin conductance responses as well as subjective evaluations of fear and expectancy of the aversive stimulation were acquired. We found that impairment of fear inhibition (extinction) in the safe context during learning (day 1) was associated with the amount of pack-years in smokers. During retrieval of fear memories (day 2), smokers showed an impairment of contextual (safety context-related) fear inhibition as compared with non-smokers. These effects were found in physiological as well as subjective measures of fear. We provide initial evidence that smokers as compared with non-smokers show an impairment of fear inhibition. We propose that smokers have a deficit in integrating contextual signs of safety, which is a hallmark of post-traumatic stress and anxiety disorders.

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INTRODUCTION

Smokers are heavily overrepresented among psychiatric patients (Cook *et al*, 2014; Lasser *et al*, 2000). In patients suffering from post-traumatic stress disorder (PTSD), the odds-ratio for smoking is between 2 and 4 (Fu *et al*, 2007) and related to symptom severity in high-risk groups, such as combat veterans (Kirby *et al*, 2008). Moreover, smoking compromises therapeutic efficiency and enhances relapse risk in PTSD and anxiety disorders after treatment (Taylor *et al*, 2015). Although several studies observed associations between smoking and categorical diagnoses of PTSD (Breslau *et al*, 2004; Fu *et al*, 2007) and other anxiety-related disorders (Isensee *et al*, 2003; Lasser *et al*, 2000), it is unclear if associations between smoking and basic

dimensional phenotypes of fear exist. Dimensional measures of fear within the Research Domain Criteria (RDoC) theorem describe the spectrum between adaptive to maladaptive responses within the negative valence systems (ie, lower-order constructs: potential and acute threat Cuthbert and Insel, 2013), where PTSD patients are considered the extreme group on the maladaptive side. An untested hypothesis is that smoking is associated with maladaptive fear responses across the dimensional spectrum in healthy populations.

Dimensional measures of fear responses and fear inhibition can be investigated with pre-clinical models that might provide insights into processes relevant for PTSD. Fear conditioning is the prototypical model for such a purpose where a neutral cue (conditioned stimulus, CS) is associated with an aversive event (unconditioned stimulus, US). In animals, acute nicotine was found to enhance conditioned fear responses (CRs) to CSs and to impair the inhibition of CRs within safe contexts (Kutlu and Gould, 2015). The inability to take advantage of such contextual safety signals may be mechanistically involved in the excessive fear

*Correspondence: Dr J Haaker, Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Hamburg 17177, Germany, Tel: +49 40 7410 59859, Fax: +49 40 7410 59955, E-mail: j.haaker@uke.de

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Figure 1 (a) Schematic illustration of the context-dependent cue conditioning and extinction paradigm, consisting of a learning phase (day 1) and a retrieval phase 24 h later (day 2). (b) CS specific responses in non-smoking and smoking participants during day 1 (learning) in the danger and safe contexts measured as skin conductance responses (SCRs), (c) subjective fear and (d) US expectancy. (e) Individual amount of cigarette consumption (pack-years) is correlated with conditioned fear responses (CRs) in the safe context during learning on day 1 measured as SCRs, (f) subjective fear and (g) US expectancy.

reactions in PTSD patients. Fear reactions to trauma-associated stimuli after trauma and the frequent relapse following exposure-based treatments strongly rely on deficient learning and/or memory about the safety of everyday contexts (Vervliet *et al*, 2013). However, how smoking is associated with fear inhibition in humans has not been studied, yet.

We employed a cued fear conditioning and extinction paradigm (day 1). Twenty-four hours later (retrieval phase, day 2), CSs were presented again both in the conditioning ('danger') and extinction ('safe') contexts (Haaker *et al*,

2015b) (Figure 1a). We hypothesized impaired inhibition of CRs in the safe context in smokers relative to non-smokers.

MATERIALS AND METHODS

Participants

In total, 376 healthy individuals (mean age: 24.5 years, SD: 3.3; 258 females) participated in the study that was part of a large behavioral test-battery. 349 participants (242 females, 22% smokers) had valid data on both consecutive days of the

Table 1 Sample Description of Smoking and Non-Smoking Participants

Variable	Mean (SD) Non-smokers	Mean (SD) Smokers	p-value
Sample size	270	76	—
Age	24.48 (3.2)	25.05 (3.5)	0.131 ^a
Gender	Females: 181 Males: 89	Females: 61 Males: 15	0.033^b
Cigarette consumption per day	—	—	—
1–10 cigarettes		N = 56 (74.7%)	
11–20 cigarettes		N = 19 (25.3%) Missing = 1	
Approximate pack-years (one pack-year equals smoking 11–20 cigarettes per day for one year)	—	4.73 (3.50)	—
Alcohol consumption (drinks/ month)	3.03 (2.8)	5.42 (3.68)	< 0.001^a
Cannabis consumption (joints/month)	0.63 (0.38)	0.71 (0.37)	0.380 ^a
Coffee consumption (cups/day)	1.03 (1.16)	1.70 (1.77)	< 0.001^a
School education			0.45 ^b
High school degree ('Mittlere Reife' or equivalent)	(N = 2, 0.7%)	(N = 2, 2.6%)	
Attended college ('Gymnasium')	(N = 3, 1.1%)	(N = 0)	
College degree ('Abitur')	(N = 12, 4.4%)	(N = 1, 1.3%)	
Attended/attending university	(N = 198, 73.3%)	(N = 56, 73.7%)	
University degree	(N = 53, 19.6%) Missing: N = 2	(N = 17, 22.4%) Missing: N = 0	
STAI trait anxiety (sum score)	36.49 (8.23)	38.05 (9.15)	0.183 ^a
TCI novelty seeking (sum score)	20.76 (5.90)	23.28 (6.23)	0.001^a
TCI reward dependence (sum score)	16.10 (4.17)	16.51 (4.07)	0.439 ^a

Sample description of smoking and non-smoking participants. Significant differences are marked bold. Controlling for individual differences in personality traits (STAI trait anxiety, TCI novelty seeking and TCI reward dependence), alcohol consumption, age, or gender did not substantially change the results in any dependent measure (context*smoking status interaction p 's < 0.02 in all analyses).

^aUnpaired t -test, two-sided.

^b χ^2 test exact, two-sided.

experiment and were included in the analyses. As such, the participants were not matched regarding smoking status and other individual differences, but rather to represent an age-specific proportion of smokers and non-smokers in Germany (Bundeszentrale für gesundheitliche Aufklärung, 2015). The effects of gender and trait anxiety in this sample have been published elsewhere (Haaker *et al*, 2015b; Lonsdorf *et al*, 2015) and current analyses controlled for their influence. Participants gave written informed consent. The study was approved by the local ethics committee in Hamburg (Ärztchamber Hamburg). Overall, 22% of the participants were smokers and were allowed to smoke freely before the experiment on both days (see Table 1 for sample description and (Haaker *et al*, 2015b) for sample and task details).

Stimuli

Two geometric symbols (circle and triangle) served as CSs presented on either a blue or yellow screen background, which served as contexts. Assignment of the symbols and the background colors were counterbalanced across participants. Stimuli were presented using Presentation Software

(NeuroBehavioral Systems, Albany California, USA). The US consisted of a train of three square-wave pulses of 2 ms each (DS7A, Digitimer, Welwyn Garden City, UK) delivered on the right dorsal hand and was individually adjusted to a level of maximum tolerable pain (subjective ratings from 0: 'I feel nothing' to 10: 'maximally unpleasant', see Table 1) before the experiment. There were no difference between smoking and non-smoking participants with regard to the US current amplitude on day 1 (non-smokers mean: 4.3 mA, SD: 5.7; smokers mean: 4.4 mA, SD: 3.70, $p > 0.97$) or day 2 (non-smokers mean: 4.4 mA, SD 5.71; smokers mean: 4.5 mA SD: 3.68, $p > 0.81$), and importantly there were no differences between groups in the subjective rating of the painfulness of the US on either day (day 1: non-smokers mean: 6.12, SD: 1.30; smokers mean: 6.16, SD: 1.23, $p > 0.81$; day 2: non-smokers mean: 6.01, SD: 1.39; smokers mean: 6.03, SD: 1.23, $p > 0.92$).

Paradigm

Fear conditioning and extinction learning was employed as a within-subject design (Figure 1a). The protocol consisted of an A₁B₁A₂B₂ design, with two interleaved blocks of fear

conditioning in one context (A_1 and A_2 : danger context) and extinction in another context (B_1 and B_2 : safe context) on day 1 (learning). Each block consisted of 12 presentations of the CS+ and the CS−, and each CS had a duration of 3 s. The intertrial interval (ITI) was jittered in duration between 2.5 and 4 s. During conditioning in the danger context, the CS+ was paired in 50% of trials with the aversive, electrotactile US (onset 2.5 s after CS+ onset), whereas the CS− was never paired with the US. During extinction in the safe context, both CSs were never paired with a US. Hence, on day 1, the CR (differential response to the CS+ > CS−) in the danger context on day 1 can be used to index learned fear, whereas the CR in the safe context provides an inverse measurement of fear inhibition, a high CR indicating a deficit in inhibition (in particular, inhibition of fear to the CS+).

On day 2 (retrieval), US intensity was individually adjusted again. This was followed by 10 interleaved blocks of each context employing an $A_1B_1A_2B_2 \dots A_{10}B_{10}$ design. Each block consisted of one presentation of both the CS+ and the CS−, but without any US presentation in both contexts. Producing a CR to a CS+ in the danger context ('renewal', Bouton, 2002; Vervliet *et al*, 2013) can be considered adaptive, given the danger context has been associated with threat on day 1. However, in the safe context, a high CR would indicate a deficit in the retrieval or expression of the fear-inhibitory memory formed during extinction in this context on day 1. Hence, an adaptive response profile on day 1 would consist in a marked differentiation of CRs as a function of context (high in danger, low in safe). We term this 'contextual fear inhibition'.

Physiological Measurements

Skin conductance responses (SCRs) were recorded as previously described (Haaker *et al*, 2015b). In short, skin conductance was recorded using a BIOPAC MP35 amplifier (BIOPAC Systems, California, USA) and self-adhesive Ag/AgCl electrodes placed on the palmar side of the left hand on the distal and proximal hypothenar eminence. Data were down-sampled to 10 Hz, phasic SCRs were automatically scored as an increase in skin conductance within 1–3.5 s after stimulus onset and raw SCR amplitudes were then logarithmized and range-corrected $[(SCR/SCR_{max})+1]$. Non-responders were defined as participants not showing any US response during the first half of the experiment (day 1) and excluded from all SCR analyses ($N=32$). Additional 24 participants were excluded from the analyses, due to missing data on one of the days. In total 290 participants were included in the SCR analyses (61 smokers). Several control analyses (see previous publication, Haaker *et al*, 2015b) confirmed that USs that preceded or followed the CS presentations did not bias SCRs on day 1.

Subjective Measurements

In addition, participants rated their stress/fear/tension evoked by the CSs as well as their US expectancy after each block (4CS+ and 4CS− trials) on day 1 and after each block (1CS+ and 1CS− trials) on day 2, by answering the questions 'When you saw the symbol, how strong was your stress/fear/tension' (for fear) and 'When you saw the symbol, to what extent did you expect the painful stimulus?' (for US

expectancy). Ratings were given on a visual analog scale ranging from 0 (none) to 100 (maximum).

Statistical Analyses

In general, only participants with valid data-points on day 1 and day 2 were included in our analyses (Fear ratings and US expectancy: $N=349$, 242 females, 22% smokers; SCR: $N=290$, 203 females, 21% smokers). CRs were analyzed using repeated-measures ANOVAs with stimulus (CS+/CS−) and context (danger/safety) as within-subject factors and smoking status as between-subject factor, separately for each day. Repeated-measures ANOVAs controlling for individual differences in novelty seeking, consumption of alcohol and coffee, as well as age and gender and anxious temperament (STAI trait anxiety) were performed separately. Pack-years approximation was calculated as the product of self-reported daily cigarette consumption (1–10 cigarettes = 0.5 packs per day; 11–20 cigarettes = 1 pack per day; 21–30 cigarettes = 1.5 packs per day) and the smoking duration (in years). Correlation between pack-years and CRs in both contexts were calculated as Pearson correlation coefficients and tested for statistical difference (Lee and Preacher, n.d.). Analyses controlling for the influence of individual differences in novelty seeking, consumption of alcohol and coffee, as well as age, gender and anxious temperament (STAI trait anxiety) were performed as linear regression models (step-wise inclusion) for day 1 and day 2. In addition, analyses exploring the moderation of smoking effects by trait anxiety were performed as linear regression models including pack-years (for day 1) or smoking status (for day 2), trait anxiety as well as the interaction of both (mean centered).

If appropriate, Greenhouse–Geisser corrections were adopted and $p < 0.05$ was considered significant.

RESULTS

Effects of Smoking on Day 1 (Learning)

On day 1, no significant differences between smokers and non-smokers were observed during either conditioning (danger context) or extinction (safe context) (no main effects of or interaction with smoking status, all p 's > 0.19, see Figure 1b–d and Supplementary Table 1 for all main effects of task). However, CRs (CS+ > CS−) in all dependent measurements were significantly correlated with pack-years in smokers in the safe context (SCR: $r = 0.348$, $p = 0.004$; fear ratings: $r = 0.301$, $p = 0.009$; US expectancy: $r = 0.316$, $p = 0.006$; Figure 1e–g), but not in the danger context (SCR: $r = 0.129$, $p = 0.30$; fear ratings: $r = 0.196$, $p = 0.094$; US expectancy: $r = 0.123$, $p = 0.12$). The correlation in the safe context was significantly stronger as compared with the danger context for the SCRs ($Z = -1.66$; p (one-tailed) = 0.049) and US expectancy ($Z = -1.89$; p (one-tailed) = 0.029). This might suggest that chronic smoking is associated with enhanced CRs during extinction learning, pointing towards a fear inhibition deficit.

The groups of smoking and non-smoking participants differed with respect to gender distribution, alcohol consumption, coffee consumption and novelty seeking (Table 1).

Control analyses that included these variables, as well as trait anxiety, as predictors in a step-wise regression of CRs

in the safe context on day 1 consistently revealed pack-years as the significant predictor across measurements (Supplementary Table 2).

Previous results within this sample (Haaker *et al*, 2015b) have revealed that inhibition of fear responses is associated with anxious temperament (trait anxiety). We tested if anxious temperament moderates the effect of pack-years on CRs in the danger and safety contexts on day 1. Indeed, the step-wise regression model revealed that the interaction between pack-years and trait anxiety was a stronger predictor for the CR in the safe context as compared with each variable alone (variable main effects), across measurements (Supplementary Table 3 and Supplementary Figure 1). This might suggest that the influence of chronic smoking on fear inhibition during extinction learning increases with increased trait anxiety.

Effects of Smoking on Day 2 (Retrieval)

At the retrieval test (day 2), a context*smoking status interaction was observed in all dependent measurements (SCRs: $F(1,289)=8.50$, $p=0.004$, $\eta^2=0.03$; fear ratings: $F(1,344)=9.15$, $p=0.003$, $\eta^2=0.03$; US expectancy: $F(1,344)=6.47$, $p=0.01$, $\eta^2=0.02$; Figure 2a–c), in the absence of a main effect of smoking status ($p>0.25$, see Supplementary Table 4 for main effects of task). This interaction resulted from attenuated contextual inhibition of CRs in the safe relative to the danger context in smokers, as compared with non-smokers, irrespective of CS type (see Figure 2d–f for *post-hoc* tests). There were no correlations with pack-years (all $p>0.1$).

Control analyses that included gender distribution, alcohol consumption, coffee consumption and novelty seeking, as well as trait anxiety, as predictors in a step-wise regression of contextual inhibition on day 2 consistently revealed smoking status as the significant predictor across measurements (Supplementary Table 5). In addition, inclusion of these variables as separate covariates still yielded robust smoking status by context interactions across all measurements on day 2 (Supplementary Table 6). Importantly, the effect of smoking status on contextual inhibition on day 2 was not moderated by trait anxiety (Supplementary Table 7). *Post-hoc* power calculation revealed that our sample size provided sufficient power to detect this effect (power >0.99 ; G*Power Version 3.1.9.2).

DISCUSSION

Our results provide converging evidence from physiological responses and subjective evaluation that smokers as compared with non-smokers show impaired fear inhibition through the retrieval of contextual signals indicating safety. In addition, during extinction learning, the amount of smoking (pack-years) was associated with the level of conditioned fear responses. Participants with more pack-years showed higher fear responses, in particular within a context that was safe (where the CS+ was no longer paired with the US). Interestingly, this effect during extinction learning was moderated by trait anxiety, which has previously been found to regulate inhibitory learning within this sample (Haaker *et al*, 2015b). By contrast, one day later,

inhibition of fear memory in the safe context was impaired in smokers as compared with non-smokers regardless of the amount of cigarette consumption and independent of trait anxiety. Hence, during learning as well as during memory retrieval, smokers showed a deficit in contextual gating of safety, which mirrors the impairment found in clinical populations diagnosed with PTSD and anxiety disorders. Interestingly, we did not observe uniform effects of smoking on learning and retrieval processes. The amount of smoking (measured in pack-years) was correlated to a deficit in extinction learning. On the other hand, retrieval of safety memory was impaired in smoking individuals, despite the amount of pack-years. This might suggest slightly different mechanisms of how smoking impairs learning, consolidation and retrieval of fear and safety.

However, within the framework of RDoc, we provide evidence that smoking is associated with deficits in the negative valence system in responses to acute threat. Although this might explain the co-occurrence of smoking and PTSD diagnoses, we suggest that this association exists in undiagnosed populations, as well.

Our participants were allowed to smoke freely before the experiments on both days, and we did not measure smoking before the experiments or nicotine status during the experiments. However, the associations observed on day 1 with a measure of long-term cigarette consumption (pack-years) indicate that our findings might be related to chronic rather than acute smoking effects.

Three mechanisms may contribute to these effects. First, being a smoker may interfere with memory consolidation or retrieval and/or related discrimination processes, possibly via nicotinic or dopaminergic mechanisms (Fu *et al*, 2007; Kutlu and Gould, 2015; Subramaniam and Dani, 2015). Although several studies found alterations of dopaminergic functioning in smokers (Bloomfield *et al*, 2014; Cosgrove *et al*, 2015; Rademacher *et al*, 2015), there is evidence that dopamine is involved in the consolidation of safety memories to inhibit the return of fear responses (Haaker *et al*, 2013, 2015a). Second, maintained smoking habits (Winkler *et al*, 2011) and a persistent conditioned fear response in safe contexts might be due to an common underlying deficit in flexibly adjusting learned associations. Third, trait anxiety might moderate the effect of smoking on fear inhibition deficits.

Previous studies examining the association between PTSD and smoking found evidence for bi-directional influence of smoking and development of PTSD (Breslau *et al*, 2004), albeit less evidence for shared genetic heritability that might explain a common underlying deficit of both (Fu *et al*, 2007; Koenen *et al*, 2005, 2006).

Our results have several limitations. Participants in this study were not matched for several individual differences (eg, gender) between smoking and non-smoking individuals. Moreover, our analysis relied on self-report of smoking status and pack-years. In particular the measurement of pack-years might not be optimal to access reliable information about chronicity of nicotine consumption. Hence, imprecisely measured confounders or the presence of unmeasured confounders cannot be ruled out in our results. Future studies will be important to replicate our findings in matched groups, using biochemical examination of smoking status (eg, levels of CO or metabolites as cotinine) and testing

Figure 2 (a) CS responses during day 2 (retrieval) reveal a context*smoking status (non-smoking vs smoking participants) interaction measured as skin conductance responses (SCRs), (b) subjective fear and (c) US expectancy. (d) During memory retrieval on day 2, smokers show less contextual inhibition of SCRs (CS+: $t(346) = 3.07$, $p = 0.002$; CS-: $t(346) = 1.54$, $p = 0.14$), (e) subjective fear (CS+: $t(346) = 3.04$, $p = 0.003$; CS-: $t(346) = 3.76$, $p < 0.001$) and (f) US expectancy (CS+: $t(346) = 2.56$, $p = 0.012$; CS-: $t(346) = 2.46$, $p = 0.015$). * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$. Error bars represent the standard error of the mean.

the effect of instructed abstinence. In addition, pharmacological studies testing the causal effect of nicotine, might help to understand the neuropharmacological mechanisms in more depth.

Although our study cannot provide causal mechanisms that explain the association between smoking and impaired fear inhibition, it might well be that influences of smoking on broader processes involved in learning, eg, attention (Ashare and Hawk, 2012; Lerman *et al*, 2001) have contributed to our results. Nevertheless, the effects observed here underline the fact that co-occurrence of smoking and deficits in fear inhibition are prevalent in undiagnosed populations. Moreover, this deficit in fear inhibition is due to impaired identification of contextual safety, in line with previous experiments of nicotine exposure in rodents (Kutlu *et al*, 2014; Kutlu and Gould, 2014).

Importantly, deficient inhibition of fear responses through contextual safety signals is a hallmark of PTSD and anxiety-

related disorders (Vervliet *et al*, 2013). Hence, our results suggest for the first time contextual inhibition of fear as a potential mechanistic link between smoking and the development and maintenance of these disorders. Prospective investigations are warranted to unravel causal relationships.

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