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Cue-induced brain activation and relapse in cigarette smokers during long-term smoking cessation treatment: a prospective fMRI study

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Abstract

Background: Studies investigating cue-induced brain activation as markers for cigarette use relapse have yet to be examined for their relevance in long-term cessation treatment. This feasibility functional magnetic resonance imaging (fMRI) investigation compared regions of cigarette cue-induced brain activation between cigarette smokers who relapsed versus those who abstained during a six-month intervention programme.

Methods: Eighteen adult cigarette smokers (>15x/day cigarette use >2 years) with tobacco use disorder completed a baseline fMRI cue exposure paradigm before undergoing treatment. Whole-brain fMRI contrasts between cue exposure conditions (cigarette, neutral) were assessed in patients who relapsed (≥1x cigarette use) compared to those who abstained during treatment. Subjective craving was assessed after each block.

Results: Nine patients relapsed (38.9 ± 6.9 years old; 4F) and nine abstained (40.3 ± 7.4; 6F) from cigarette use. Relative to abstainers, patients who relapsed exhibited greater activation in parietal, fusiform, cingulate, prefrontal, orbitofrontal, and supplementary motor area regions. There were no group differences in craving.

Conclusion: Cue-elicited brain activation associated with cigarette use relapse during treatment was observed in areas involved in value-driven attention. Cue-related neural activation in these areas may be potential vulnerability markers for cigarette use relapse during long-term interventions. Given the promising results in this small pilot, further investigations are warranted.

Keywords

fMRI, Cue Reactivity, Smoking Cessation Treatment, Relapse, Tobacco

INTRODUCTION

Cigarettes can be immensely difficult to quit. Even with formal treatments, most attempts to quit result in relapse (Piasecki, 2006; Potvin, Tikàsz, Dinh-Williams, Bourque, & Mendrek, 2015). Craving is a defining feature of tobacco use disorder and a key predictor of relapse to cigarettes (Potvin et al., 2015). Neuroimaging studies have explored brain regions involved in cue-induced cigarette craving, identifying regions subserving attention and motivational functions, for example, visual, orbito- and pre-frontal, cingulate, striatal and insular regions (Potvin et al., 2015), but limited evidence supports the relevance of these cue-induced activations as a potential marker for cigarette use relapse risk during smoking cessation. Abstinence outcomes in cigarette use studies vary; while some focus on short-term abstinence after a designated quit date, longer-term endpoints (six to twelve months) recommended by the Society for Research on Nicotine and Tobacco (SRNT) offer more stable and valid estimates of long-term outcomes (Pierce & Gilpin, 2003).

Evidence suggests there may be qualitatively different determinants of early versus late (in other words, occurring six months or more after abstinence) cigarette use relapse. For instance, some predictors of cigarette use relapse have been shown to change depending on the amount of time since abstinence was initiated (Dijkstra,

Borland & Buunk, 2007; Piasecki, 2006; Vangeli, Stapleton & West, 2010). Additionally, first-line cessation treatments are generally more effective at achieving short-term, but not long-term, abstinence (Piasecki, 2006). It is necessary to investigate cue-induced markers of relapse for long-term outcomes to encompass individuals who, potentially via different mechanisms, experience delayed relapse.

To date, six treatment studies involving functional neuroimaging have examined cigarette cue exposure and relapse in cigarette smokers (Allenby et al., 2020; Gilman et al., 2018; Janes et al., 2017; Janes et al., 2010; Owens et al., 2018; Versace et al., 2014). Those examining brain structures based on *a priori* regions of interest, such as the anterior cingulate cortex (ACC), insula, striatum and prefrontal cortex, revealed cue-induced activation patterns related to relapse within nine-week (Owens et al., 2018) and twelve-week (Gilman et al., 2018; Janes et al., 2017; Versace et al., 2014) outpatient treatment (with one study including a three- and six-month post-quit follow-up; Versace et al., 2014). Others employed whole brain contrasts and identified areas, such as ACC, insular and striatal activity involved in cigarette cue-related relapse vulnerability following a short seven-day (Allenby et al., 2020) and eight-week (Janes et al., 2010) outpatient programme. While these findings elucidate cue-induced markers of relapse vulnerability during treatment, no study has assessed cue response patterns associated with relapse during an extended period of active smoking cessation and therapy.

The present pilot study employed whole-brain neuroimaging of cue-induced activation associated with cigarette use relapse among adult cigarette smokers undergoing a six-month cognitive behavioural therapy (CBT)-based smoking cessation programme. Our objectives were to (1) examine the feasibility of integrating longitudinal relapse endpoints with neuroimaging in the context of a treatment study, and (2) generate preliminary evidence on whether smokers who relapse during long-term treatment exhibit differential whole-brain activation to cigarette cues compared with those who maintain abstinence. We hypothesised that smokers who relapsed during treatment would show a differential pattern of activation in response to cigarette cues relative to those who maintained abstinence.

METHODS

Participants

Eighteen adults participated in a six-month CBT-based smoking cessation programme at the University of Bonn. Volunteers were eligible to participate in the fMRI subproject if they: (1) were right-handed (2) smoked ≥15 cigarettes daily for ≥2 years, (3) scored >85 for premorbid IQ (National Adult Reading Test – German version), (4) met DSM-IV criteria for nicotine dependence (American Psychiatric Association, 2000), (5) met no other current Axis I disorder, (6) had no history of psychosis, mania/hypomania, substance use disorders, or a neurologic condition, and (7) were not taking any central nervous systems medications. All structured clinical interviews were conducted by an experienced psychiatry resident.

Participants had to abstain from using alcohol or psychoactive medications for ≥24 hours, caffeine for ≥6 hours, and cigarettes for ≥4 hours before the MRI scan (verified via carbon monoxide (CO) monitor). Participants were told that they could smoke a cigarette immediately after the MRI assessment.

Experimental protocol

Participants completed a single MRI session immediately after completing a package of self-report questionnaires assessing subjective stress, symptoms of depression and severity of nicotine dependence.

The cue-reactivity fMRI paradigm was designed in a blocked fashion, presenting two cue conditions in pseudo-randomised order. A 30-second video clip was shown in each of the twelve blocks, with six presenting cigarette smoking cues (C) and the other six showing non-smoking-related neutral content (N). Participants rated subjective craving on a visual analogue scale (1 = "no craving" to 10 =

"very high craving") immediately after each block.

Participants set a "quit day" that took place within two weeks of completing the MRI protocol and marked the start of their six-month smoking cessation programme. The CBT-based programme comprised 20 group sessions led by a licensed psychologist, with optional nicotine patches for the first six weeks of treatment. In group sessions, participants received a structured self-help manual which they used to support cessation efforts between meetings. The manual content was reviewed during sessions, where alternative behaviours to smoking were also developed and practised. Smoking status was confirmed via CO-monitor at the start of each group meeting. Any reinstatement of cigarette use was documented as a relapse.

The fMRI examinations were performed on an Achieva 3.0T MRI system (Philips, Best, Netherlands), using a quadrature transmit-receive headcoil (TE/TR/Flip = 35/3000/90°; FOV = 230 x 230 mm^2; 41 transversal slices, spatial resolution 3.5×3.5×3.5 mm^3).

After acquisition of the fMRI data, a high-resolution T1-weighted anatomic scan (1×1×1 mm) was acquired according to a standard clinical protocol.

Data preprocessing and analysis

The fMRI data was preprocessed and analysed using Statistical Parametric Mapping Software (SPM2; Wellcome Department of Cognitive Neurology, London, UK). The preprocessing included slice timing correction, motion correction and realignment to adjust for rigid head movements, normalisation of the images into standard Talairach space, and spatial smoothing using a Gaussian kernel of 12 mm at half maximum (FWHM).

The first-level analysis used a general linear model (GLM), with each condition modelled as a boxcar function convolved with a canonical hemodynamic response function, including its temporal derivative to account for variability in response timing. Voxel-wise statistics were computed using a univariate ANOVA framework to estimate contrasts for cigarette versus neutral (*C–N*) cues.

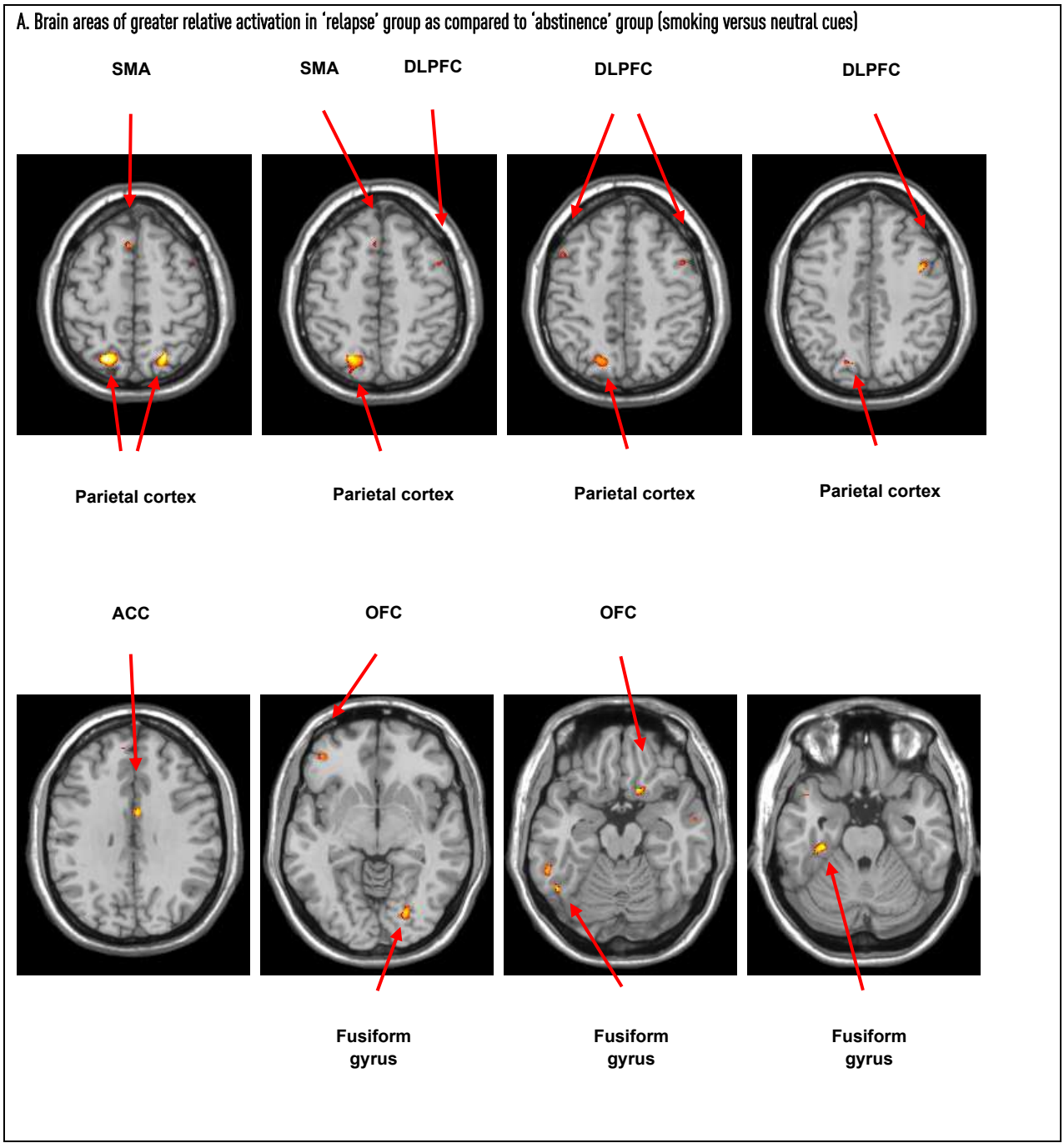
The resulting contrast images were carried over to a second-level random effects analysis: to infer group differences between relapsed smokers and abstinent smokers, we compared these groups with voxel-wise two-sample t-tests ($p<.005$, uncorrected; extent threshold: $k \geq 10$ voxels). T-tests were used to probe for group differences on self-report measures, including craving. Demographic variables such as sex and age were not included as covariates due to the small sample size, which limits power and increases the risk of overfitting. Additionally, in previous studies using similar cue-reactivity paradigms, these variables have not been found to differ between individuals who relapsed and those who maintained cigarette abstinence (Janes et al., 2017; Versace et al., 2014).

RESULTS

At the six-month follow-up, nine patients relapsed (38.9 ± 6.9 years old; 4 females) and nine (40.3 ± 7.4 years old; 6 females) maintained abstinence during treatment. There were no group differences on symptom severity for depression and nicotine dependence, subjective stress or self-reported craving. Craving ratings were generally low across the sample (relapsed: 2.9 ± 1.7; abstained: 2.3 ± 2.0).

Group comparison for *C-N* contrast revealed that the relapse group exhibited greater activation in the superior parietal cortex (bilateral), fusiform gyrus (bilateral, especially left), right anterior cingulate (ACC), dorsolateral prefrontal cortex (DLPFC, bilateral), lateral (left) and medial (right) orbitofrontal cortex (OFC) and left SMA relative to the abstinence group (Figure 1). The greatest difference in peak activation was in the bilateral parietal cortex, left fusiform gyrus and right ACC.

Figure 1. fMRI analysis of brain activation during exposure to smoking cues versus exposure to neutral cues



B. Significance parameters and peak coordinates of brain areas shown in A.

Region		k_E [a]	T	p (uncorrected)	Peak coordinates [b] x	y	z
Parietal cortex	Left	224	4.48	0.000	-20	-62	54
	Right	48	4.38	0.000	24	-62	54
Fusiform gyrus	Left (anterior)	42	4.14	0.000	-32	-26	-18
	Left (posterior)	30	3.82	0.001	-48	-56	-12
	Right	44	3.81	0.001	24	-74	-2
ACC	Right	27	4.04	0.000	4	2	30
OFC	Left (lateral)	30	3.54	0.001	-40	42	-6
	Right (medial)	37	3.89	0.001	14	18	16
DLPFC	Left	16	3.17	0.003	-46	16	44
	Right	51	3.81	0.001	42	6	40
SMA	Left	19	3.42	0.002	-4	22	50

a. Abbreviations: kE = cluster size; ACC = anterior cingulate cortex; OFC = orbitofrontal cortex; DLPFC = dorsolateral prefrontal cortex; SMA = supplemental motor area.

b. Peak coordinates were rounded following conversion from MNI coordinates into Talairach coordinates.

DISCUSSION

The present study investigated differences in regional activation in response to laboratory cue exposure among patients who relapsed versus those who did not relapse to cigarette use over the course of a six-month CBT-based smoking cessation programme. Consistent with our hypothesis, there were differences in regional activation in response to cigarette cue exposure among patients who relapsed versus those who remained abstinent. The most pronounced differences in activation were observed in parietal and fusiform regions, followed by ACC, OFC, DLPFC and SMA. There were no group differences in cravings.

Heightened parietal, fusiform and ACC reactivity have been previously associated with cue-induced relapse in smokers (Allenby et al., 2020; Janes et al., 2010). These regions have been implicated in attentional bias towards smoking cues (Elton, Chanon & Boettiger, 2019). The frontal cortical areas are, due to their prominent role in behavioural control and inhibition, frequently implicated in craving (Potvin et al., 2015). The DLPFC, central to response inhibition, has been previously linked to relapse (Versace et al., 2014), while the OFC is involved in salience processing that guides reward-based decision-making (Potvin et al., 2015). Moreover, cue-induced primary and pre-motor activity has been linked to relapse in smokers (Janes et al., 2010), potentially reflecting a cue-elicited preparatory response to consume cigarettes (Smolka et al., 2006). The SMA, more specifically, has shown to be involved

in linking action with internal motivational states (Nachev, Kennard & Husain, 2008).

Congruent with prior reports, there was a lack of group differences in cue-related subjective craving (Owens et al., 2018; Versace et al., 2014), and, in general, self-reported craving shows little consistency with cue-induced neural activation or smoking cessation outcome (Perkins, 2012). As there is some evidence to support distinct mechanisms between early versus late cigarette use relapse (Piasecki, 2006), observed OFC and SMA activations in those who relapsed over a longer treatment duration (six months) may suggest a potential link to susceptibility for delayed relapse. Further research is needed to directly assess whether neural markers of early versus late relapse can be distinguished, allowing for a better understanding of clinically relevant subgroups and potential targeted interventions.

Some limitations of this study are discussed. First, our small sample size limits the power to conduct deeper analyses, including the effects of individual factors on the observed outcomes. Given this was beyond the scope of a pilot, investigations based on a larger sample size may validate the initial findings and further assess potentially relevant subgroups (for example, symptom severity). Second, we did not document the use of nicotine patches, which were offered for the first six weeks of treatment. It is possible that differential use of nicotine substitution may have influenced patient relapse status. Lastly, there were more females in the relapse group (67%) than males. As cue-activated networks have been shown to differ by sex (Potvin et al., 2015), larger investigations on potential sex differences in neural cue reactivity and its relationship to treatment-related outcomes are warranted.

Limitations notwithstanding, this is the first study to assess neural patterns of cigarette cue-induced relapse during a long-term cessation attempt. Our results provide preliminary evidence of cue-related OFC and SMA activations associated with long-term smoking cessation outcomes. We are encouraged by these findings, which validate previous studies and provide new regions of interest, despite the small sample size. These initial data support the feasibility of using fMRI to assess cue-related neural activation as a potential marker of relapse in smokers over extended treatment periods. The specific regions appear to be of potential clinical relevance for attention and motivation. These findings are intended to inform the design of larger-scale trials aimed at establishing reliable neuroimaging markers of long-term relapse risk. Broader investigations are needed to confirm and extend findings, including individuals who use other substances.

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Conflict of interest: the authors declare that they have no conflict of interest.

Data availability: the datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical statement: the study protocol was approved by the ethics board of the University of Bonn.

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Informed consent: all participants provided written informed consent before participation in the study.

Study registration: this study is not a registered clinical trial.

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