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ORIGINAL ARTICLE

Tobacco smoking in schizophrenia: investigating the role of incentive salience

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Background. Smoking is highly prevalent in people diagnosed with schizophrenia, but the reason for this co-morbidity is currently unclear. One possible explanation is that a common abnormality underpins the development of psychosis and independently enhances the incentive motivational properties of drugs and their associated cues. This study aimed to investigate whether incentive salience attribution towards smoking cues, as assessed by attentional bias, is heightened in schizophrenia and associated with delusions and hallucinations.

Method. Twenty-two smokers diagnosed with schizophrenia and 23 control smokers were assessed for smoking-related attentional bias using a modified Stroop task. Craving, nicotine dependence, smoking behaviour and positive and negative symptoms of schizophrenia were also recorded.

Results. Both groups showed similar craving scores and smoking behaviour according to self-report and expired carbon monoxide (CO), although the patient group had higher nicotine dependence scores. Attentional bias, as evidenced by significant interference from smoking-related words on the modified Stroop task, was similar in both groups and correlated with CO levels. Attentional bias was positively related to severity of delusions but not hallucinations or other symptoms in the schizophrenia group.

Conclusions. This study supports the hypothesis that the development of delusions and the incentive motivational aspects of smoking may share a common biological substrate. These findings may offer some explanation for the elevated rates of smoking and other drug use in people with psychotic illness.

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Introduction

People who are diagnosed with schizophrenia are typically more likely to use dependence-forming drugs, including tobacco, than the general population (de Leon & Diaz, 2005). Smoking is a major cause of cardiovascular disease in schizophrenia (Kelly *et al.* 2011), which causes two-thirds of premature deaths in these individuals (Hennekens *et al.* 2005). An improved understanding of the factors underpinning tobacco use is therefore crucial to improve the roughly 15-year reduction in life expectancy associated with this illness (Hennekens *et al.* 2005).

Cues associated with drug use, such as the sight of a cigarette packet or someone smoking, are thought be important in the development and maintenance of addictive behaviour. For example, substance users typically attribute these cues with incentive salience, reflecting a 'want' rather than a 'liking' of the drug (Robinson & Berridge, 1993). This process is driven by associative learning between cues and sensitized dopamine release but can be amplified by physiological changes such as abstinence (Robinson & Berridge, 1993). The ability of drug cues to grab attention or 'attentional bias' is commonly used as an index of incentive salience (Field & Cox, 2008) and is thought to play a causal role in drug use (Franken, 2003). Attentional bias may be an important neurocognitive index of addictive behaviour because it can prospectively identify whether an individual who smokes is likely to succeed during an attempt to quit (Waters *et al.* 2003; Janes *et al.* 2010; Powell *et al.* 2010). However, the relationship between attentional bias and smoking in schizophrenia has not yet been investigated.

The concept of salience attribution outlined by Robinson & Berridge (1993) has also been applied to schizophrenia research (Heinz & Schlagenhauf, 2010).

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It has been hypothesized that psychosis may arise from context-independent dopamine release, allowing irrelevant stimuli and internal representations to take on motivational significance (Kapur, 2003). Delusions arise as a way of explaining the subjective experience of increased salience, whereas hallucinations come from the aberrant assignment of salience to normal internal experiences (Kapur, 2003). When compared to control subjects, attribution of motivational salience to irrelevant stimulus characteristics is elevated in first-episode psychosis (Murray *et al.* 2007), in schizophrenia (Jensen *et al.* 2007) and in people at ultra-high risk of developing psychosis (Roiser *et al.* 2012). These at-risk individuals also showed an abnormal relationship between dopamine synthesis capacity in the striatum and hippocampal activation to irrelevant stimulus features during the task (Roiser *et al.* 2012). Furthermore, in a sample of patients diagnosed with schizophrenia, Roiser *et al.* (2009) found evidence of aberrant salience attribution in people currently suffering from delusions when compared to those who were not. Taken together, these findings suggest that aberrant salience attribution to irrelevant stimuli is associated with the development of psychotic symptoms (perhaps delusions in particular) and that it may be associated with changes in dopamine function (Kapur, 2003).

Similarities between the neural correlates of repeated drug use and schizophrenic illness have been suggested as an explanation for their substantial co-morbidity (Tsapakis *et al.* 2003), and erroneous salience attribution processes in addiction and psychosis are built on a common psychological framework (Robinson & Berridge, 1993; Heinz & Schlagenhauf, 2010). According to the primary addiction hypothesis (Chambers *et al.* 2001), a single neural abnormality might cause psychotic symptoms to emerge due the attribution of salience to irrelevant stimuli (Gray *et al.* 1991), but could also independently enhance the incentive motivational properties of drugs and their associated cues. This abnormality, proposed to arise in the hippocampal formation and prefrontal cortex, would thus mimic pathological changes that would only normally be achieved through chronic drug abuse (Robinson & Berridge, 1993; Jentsch & Taylor, 1999).

Induction of this abnormality in rats using neonatal ventral hippocampus lesions can model aspects of schizophrenia (Tseng *et al.* 2009) and increase self-administration of and sensitization to drugs, including nicotine (Berg & Chambers, 2008; Berg *et al.* 2013). Additionally, findings from a human chronic ketamine model of psychosis support the idea that the attribution of salience to drug-related cues and irrelevant stimulus features coincide with each other (Freeman *et al.* 2012). This suggests that individuals with schizophrenia or severe psychotic symptoms may be more prone to attribute drug-related cues with incentive salience and develop problematic drug use. Previous studies have found that control and schizophrenia smoking groups show equal levels of 'cue reactivity', or the increase in tobacco craving following exposure to smoking cues (Fonder *et al.* 2005; Tidey *et al.* 2008). However, it is not yet known whether these groups exhibit differences in salience attribution, as indexed by attentional bias, and whether this effect is linked to psychotic symptoms.

The aim of the present study was to investigate the relationship between incentive motivational processes in both nicotine dependence and schizophrenia. Based on the primary addiction hypothesis (Chambers *et al.* 2001) and a putative link between salience attribution in addiction and psychosis (Robinson & Berridge, 1993; Heinz & Schlagenhauf, 2010), we predicted, first, that smokers with a diagnosis of schizophrenia would show a stronger attentional bias towards smoking cues than a control group of smokers with a similar history of and current exposure to nicotine. Second, we predicted that attentional bias would be positively associated with the severity of delusions and hallucinations because of their hypothesized association with aberrant salience (Kapur, 2003).

Method

Design and participants

A between-subjects design compared 22 smokers with a diagnosis of schizophrenia (SS) with 23 control smokers (CS). Inclusion criteria were age 18–75 years, smoking $\geqslant 5$ cigarettes/day, agreement to abstain from alcohol and any other recreational drugs on the day of testing, normal or corrected to normal vision, and fluent spoken English. Exclusion criteria were current use of nicotine replacement therapy or other smoking cessation medication. SS were required to have a current diagnosis of schizophrenia, and CS were excluded if they reported any current or history of a major Axis 1 disorder, or a current or history of psychotic disorder in any immediate family member. All participants provided written, informed consent. This study was approved by the local National Health Service (NHS) and University College London (UCL) Research Ethics Committees and was conducted in accordance with the Declaration of Helsinki.

Assessments

Craving scales

The following questions were administered to measure tobacco craving: 'How much do you want to smoke a

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cigarette right now?' and 'How much would you enjoy a cigarette if you smoked right now?' Answers were given on 100-mm visual analogue scales (VAS) scales from 'Not at all' to 'Very much so'. These scales were administered at the beginning and the end of the testing session.

Modified Stroop task (Powell et al. 2010)

This task required participants to name the colour of 88 words that were either neutral or smoking related. Stimuli were presented in blocked format on test cards that were administered separately in a counterbalanced order. This format was chosen because it is brief, easy to administer and predictive of cessation success in smokers from the general population (Powell *et al.* 2010). Slower response times and more errors when naming smoking-related words compared to neutral words are indicative of attentional bias.

Fagerström Test for Nicotine Dependence (FTND; Heatherton et al. 1991)

This test consists of six items rated between 0 and 3, with scores ranging from 0 (low dependence) to 10 (high dependence). Internal reliability scores (Cronbach's α) were 0.711 in SS and 0.525 in CS.

Motivation To Stop Scale (MTSS; Kotz et al. 2012)

A single-item scale, this measures an individual's motivation to quit smoking, combining aspects of desire and intention to quit. Scores range from 1 (I don't want to stop smoking) to 7 (I really want to stop smoking and intend to in the next month).

National Adult Reading Test (NART; Nelson, 1991)

This task requires participants to read 50 irregular words. Full-scale IQ was estimated based on the number of errors (Nelson, 1991).

Clinical assessment

The Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984*b*) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984*a*) were administered to SS. Sums of global SAPS and SANS scores are calculated by summing the global scores for each symptom dimension (SAPS: hallucinations, delusions, bizarre behaviour, positive formal thought disorder; SANS: avolition-apathy, anhedonia-asociality, attention). Current diagnosis of schizophrenia was confirmed using ICD-10 criteria (WHO, 1993). Assessments were conducted by members of the study team (T.P.F., B.O., L.A.N. and S.L.M.) who were aware of the study aims and were trained by the lead author (T.P.F.) using the guidelines provided by Andreasen (1984*a*,*b*) and the World Health Organization (WHO, 1993). CS completed the Oxford–Liverpool Inventory of Feelings and Experiences (O-LIFE; Mason *et al.* 2005), which is designed to measure psychosis-proneness in the general population.

Procedure

SS were recruited and assessed during their regular clozapine clinic visits, and were all medicated with clozapine at the time of testing. Following initial identification and screening, a suitable test day was arranged based on a future clinic appointment. After their clinic appointment, which typically lasted 15 min, participants gave informed consent, and testing commenced in a quiet room. To control for the effect of this delay on tobacco satiation, CS were asked to refrain from smoking for at least 15 min before they provided consent and testing began. Following assessment of breath carbon monoxide (CO; Bedfont Micro Smokerlyzer, UK), both groups completed the tasks in the following order: craving scales, MTSS, modified Stroop task, NART, FTND, craving scales. Afterwards, SS were assessed on the SAPS and the SANS, and control smokers completed the O-LIFE.

Statistical analysis

All analyses were carried out using SPSS version 19 (SPSS Inc., USA). Independent-sample *t* tests (Mann–Whitney *U* tests where data violated assumptions of homogeneous variance) and χ^2 tests were used to compare groups on demographic and questionnaire-based variables. Repeated-measures ANOVA models with a between-subject factor of group (SS, CS) were used for the remaining analyses and included within-subject factors of time (pre, post) for Craving scales and stimulus type (smoking, neutral) for the Stroop task. Two-tailed Pearson correlational analyses were used to test our hypothesis that these scores would be associated specifically with delusions and hallucinations in SS. Attentional bias was also subjected to correlational analysis with expired CO, an objective measure of tobacco exposure, because it has been found to be the best predictor of attentional bias in 'healthy' tobacco smokers (Vollstädt-Klein *et al.* 2011). Dose of clozapine in SS and variables revealing group differences were subjected to exploratory correlational analyses to assess their inclusion as covariates. For all tests, a p value $\leqslant 0.05$ was considered statistically significant.

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Table 1. *Demographics, smoking behaviour and symptoms*

	Smokers diagnosed with schizophrenia (SS)	Control smokers (CS)	χ^2/t
Gender (M/F)	14/8	15/8	$\chi^2_1=0.012$
Age (years)	38.14±9.38	36.35±10.80	$t_{43}=0.592$
NART full-scale IQ	108.53±9.68	114.83±5.39	$U=140.50$*
Years smoked	19.66±8.76	18.67±10.92	$t_{43}=0.333$
Cigarettes per day	18.39±10.78	13.89±7.40	$t_{43}=1.637$
Last smoked (min)	54.78±32.97	50.65±55.23	$t_{43}=0.302$
Expired CO (ppm)	12.76±7.54	12.43±6.36	$t_{42}=0.156$
FTND	6.09±2.47	3.83±2.01	$t_{43}=3.380$**
MTSS	3.29±2.05	3.27±2.03	$t_{41}=0.983$
Tried to quit (yes/no)	18/4	19/4	$\chi^2_1=0.005$
Quit attempts	2.92±2.08	4.08±5.39	$t_{35}=0.856$
Maximum quit time (days)	298.58±565.05	481.16±761.45	$t_{35}=0.824$
Daily clozapine dose (mg)	413.64±163.25		
SAPS sum of global subscale scores	8.55±2.89		
SANS sum of global subscale scores	7.41±3.54		
O-LIFE Unusual Experiences		4.09±3.37	
O-LIFE Cognitive Disorganization		5.35±2.93	
O-LIFE Introvertive Anhedonia		2.61±2.19	
O-LIFE Impulsive Non-conformity		3.39±2.25	

M, Male; F, female; NART, National Adult Reading Test; CO, carbon monoxide; FTND, Fagerström Test for Nicotine Dependence; MTSS, Motivation to Stop Scale; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; O-LIFE, Oxford–Liverpool Inventory of Feelings and Experiences.

Data shown are number or mean±standard deviation.

* $p=0.01$, ** $p=0.002$.

Results

Participants and demographics (Table 1)

The groups did not differ in gender or age but SS had lower estimated verbal IQ scores than CS on the NART and scored higher in nicotine dependence on the FTND. However, the groups were similar on all other smoking-related variables: years smoked, cigarettes/day, time since last cigarette, expired CO, MTSS scores, number of people who had previously tried to quit, and number and duration of quit attempts. MTSS scores were missing for one SS and CS because they responded with 'I don't know'; one SS was unable to provide an expired CO reading because of an inability to hold their breath, due to lung disease; Craving scale scores were missing for one CS; and Stroop response time data were missing for one SS. As neither FTND nor NART scores correlated with change in craving scales or Stroop interference (all p's>0.05), they were not used as covariates in further analyses.

Craving scales

For the question 'How much do you want to smoke a cigarette right now?', a significant effect of time was found ($F_{1,42}=11.003$, $p=0.002$, $\eta^2_p=0.208$; Fig. 1*a*), reflecting an increase in scores across the testing session, but there were no other significant effects or interactions. A significant effect of time was also found for 'How much would you enjoy a cigarette if you smoked right now', with no interaction by group ($F_{1,42}=4.523$, $p=0.039$, $\eta^2_p=0.97$; Fig. 1*b*). No other significant effects or interactions emerged.

Modified Stroop task (Fig. 2)

Main effects of stimulus type ($F_{1,42}=14.582$, $p<0.001$, $\eta^2_p=0.258$) and group ($F_{1,43}=22.786$, $p<0.001$, $\eta^2_p=0.343$) were found for response times (Fig. 2*a*), reflecting slower responses to smoking-related words compared to neutral words, and in SS compared to CS. No significant type×group interaction was found. Error scores were at floor level and did not reveal any significant effects or interactions (Fig. 2*b*).

Correlations with attentional bias

In SS, response time interference scores correlated with the severity of delusions (mean=3.00, S.D.=1.66; $r=0.530$, $p=0.013$; Fig. 3) but not hallucinations (mean=3.32, S.D.=1.21; $r=0.349$, $p=0.121$) or any other

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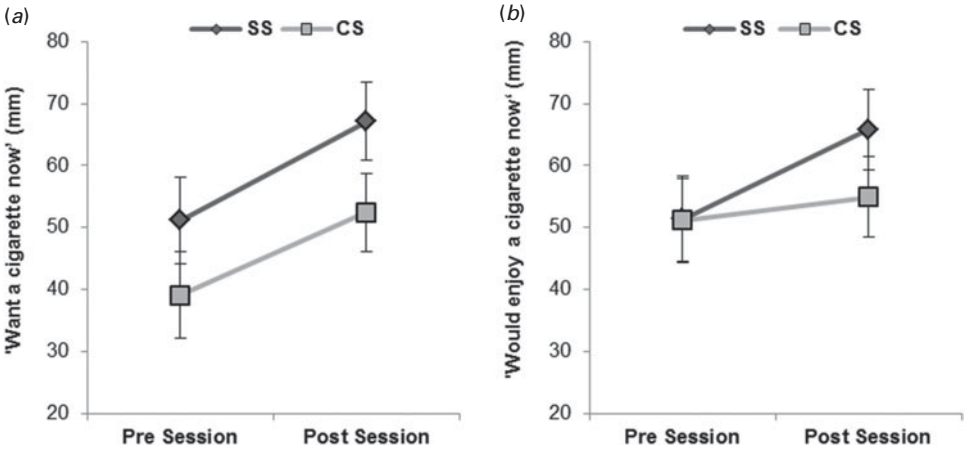

Fig. 1. Craving scales. Scores for (*a*) 'want a cigarette now' and (*b*) 'would enjoy a cigarette now' increased across the testing session for both control smokers (CS) and smokers diagnosed with schizophrenia (SS).

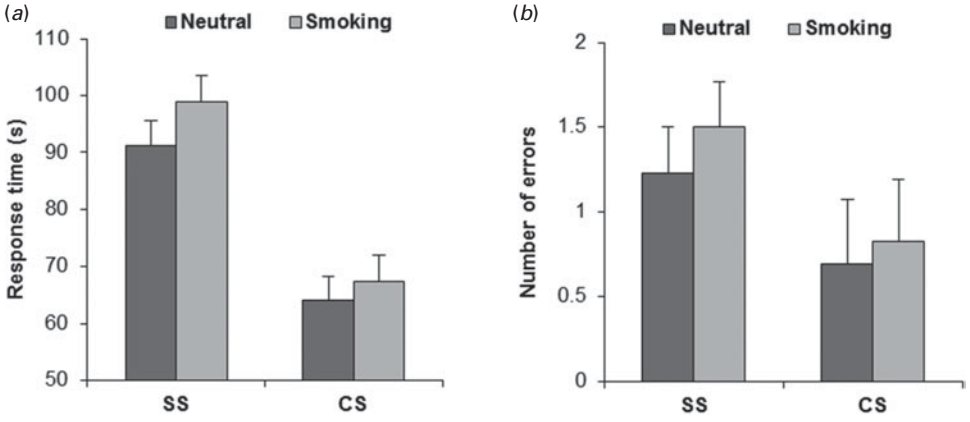

Fig. 2. (*a*) Response times on the modified Stroop task were slower in smokers diagnosed with schizophrenia (SS) than control smokers (CS) and in both groups to smoking-related compared to neutral words, indicating attentional bias towards smoking cues. (*b*) Errors on this task were low, and were equivalent across groups and conditions.

SAPS or SANS global scores, clozapine dose in SS, or with schizotypy subscales in CS. However, across both groups these interference scores showed a positive but modest relationship with expired CO, an objective index of recent tobacco exposure (r=0.343, p=0.024; Fig. 4).

Discussion

This study aimed to test the hypothesis that smokers diagnosed with schizophrenia attribute smoking cues with greater salience than control smokers, and that this effect is associated with the severity of delusions and hallucinations. Both groups showed equivalent levels of interference from smoking cues on a modified Stroop task. Within the schizophrenia group, the degree of this attentional bias was associated with the severity of delusions but not hallucinations.

A disruption of incentive motivational processing is evident in drug addiction and also in psychosis, with both disorders being characterized by changes in salience attribution (Robinson & Berridge, 1993; Kapur, 2003; Heinz & Schlagenhauf, 2010). The existence of a common abnormality giving rise to both conditions could explain why use of dependence-forming drugs, including tobacco (de Leon & Diaz, 2005), is typically elevated in people diagnosed with schizophrenia (Chambers *et al.* 2001). The findings of this study did not support this hypothesis, as similar levels of attentional bias were found in CS and SS. Those in the patient group were slower on both parts of the task but the relative difference between naming times was similar in both groups. These findings differ from those of a previous study (Copersino *et al.* 2004) reporting an absence of cocaine-related attentional bias in a schizophrenic population. However, this might be explained by the lower levels of cocaine craving in

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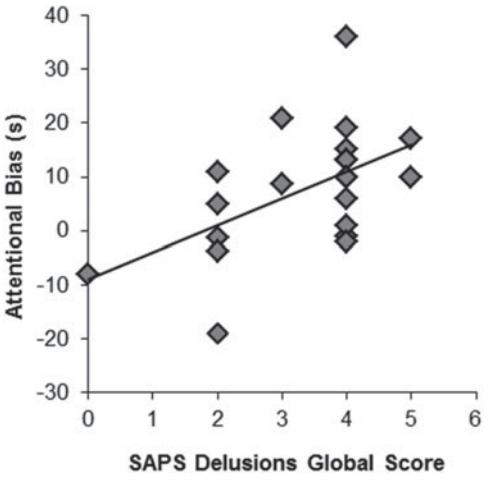

Fig. 3. Attentional bias, as measured by response time interference on the modified Stroop task, correlated with the Scale for the Assessment of Positive Symptoms (SAPS) severity of delusions score in smokers diagnosed with schizophrenia ($r=0.530$).

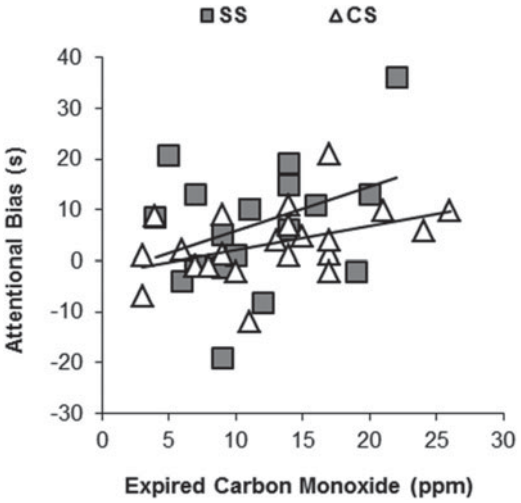

Fig. 4. Attentional bias correlated positively with expired carbon monoxide (CO) across all participants. Top line: smokers diagnosed with schizophrenia (SS: $r=0.368$); bottom line: control smokers (CS: $r=0.435$).

the schizophrenia group at baseline, which would be expected to coincide with reductions in attentional bias (Franken, 2003; Field *et al.* 2009). In our study, tobacco craving scores were similar in both groups and showed an equivalent increase across the testing session. Although we did not index craving before and after exposure to neutral and smoking words separately, our findings are consistent with a previous study using this approach in a cue reactivity design (Tidey *et al.* 2008).

Evidence for a common mechanism underpinning psychosis and the incentive motivational effects of abused drugs was, however, supported by our findings that the severity of delusions correlated with attentional bias, with 28% of the variance shared between these two measures. By contrast, the severity of hallucinations was not associated with performance on the task. These findings echo previous findings by Roiser *et al.* (2009, 2012) that aberrant salience attribution was associated with the severity of delusions but not hallucinations in medicated patients diagnosed with schizophrenia (Roiser *et al.* 2009) and with abnormal thought content in people at risk of developing psychosis (Roiser *et al.* 2012). Increased midbrain activation towards neutral *versus* aversive conditioned stimuli was also positively related to severity of delusions but not hallucinations in people with psychotic illness (Romaniuk *et al.* 2010). Taken together, these findings suggest that the attribution of salience to external cues may be linked to delusions whereas hallucinations may arise through a different mechanism (Kapur, 2003).

Of course, the association we found between attentional bias and delusions does not imply that they will always coincide with each other. Clearly, attentional bias can occur in the absence of psychosis, as found in the control group here and in many other studies (Field & Cox, 2008). In addition, the two groups did not differ in attentional bias overall. This latter finding is also consistent with Roiser *et al.* (2009), who found no differences in aberrant salience attribution when comparing medicated patients with controls at a group level. Our findings indicate that any overlap between addiction and psychosis may be particularly evident in terms of delusions. The concept of 'salience' can be applied across diagnostic categories (van Os, 2009) and our results may offer some explanation for why smoking prevalence is elevated across psychotic disorders in general, rather than exclusively in schizophrenia (Kotov *et al.* 2010).

The existence of a common abnormality that can give rise to psychosis and addictive behaviour is in agreement with evidence from a study using a chronic ketamine model of psychosis (Freeman *et al.* 2012). Ketamine users with symptoms of both drug dependence and subclinical delusional ideation showed a loss of associative blocking (a process related to psychosis) (Jones *et al.* 1992), and susceptibility to drug-related cues (a process related to drug dependence) (Freeman *et al.* 2012). Chambers *et al.* (2001) hypothesized that a common basis for both processes might arise from the hippocampal formation and prefrontal cortex, resulting in a change in the impact of dopamine release within the nucleus accumbens. A relationship between prefrontal or hippocampal brain activation and the dopamine system has been reported for both smoking-related attentional bias (Luijten *et al.* 2012) and aberrant salience attribution in people

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at ultra-high risk of developing psychosis (Roiser *et al.* 2012). If these processes do share a common underlying basis and are not causally related to each other (i.e. psychosis enhancing drug use, or *vice versa*; Tsapakis *et al.* 2003), then in cases of dual diagnosis, drug addiction should be seen as a primary disease symptom and amenable to treatment in its own right (Hahn *et al.* 2013), contrary to ideas of self-medication (Kumari & Postma, 2005). Nicotine dependence seems to have multifactorial causes in schizophrenia (Krishnadas *et al.* 2012; Wing *et al.* 2012) and the attribution of salience to smoking cues may be an additional factor, particularly in those actively suffering from delusions.

Given that smoking is highly prevalent and a major cause of premature death in schizophrenia (de Leon & Diaz, 2005; Kelly *et al.* 2011), the extent to which certain antipsychotics influence smoking should be of key importance when choosing an appropriate drug. Although the dopamine D_2 receptor antagonist haloperidol is an effective antipsychotic (Irving *et al.* 2006), it can also increase levels of smoking in tobacco users (Dawe *et al.* 1995), including those with schizophrenia (McEvoy *et al.* 1995*a*). However, because it can attenuate attentional bias and associated brain activation in drug users (Franken *et al.* 2004; Luijten *et al.* 2012), use of this drug may be preferable in certain individuals who excessively attribute incentive salience to smoking-related cues.

Atypical antipsychotics, with lower affinity for dopamine receptors than haloperidol and other typical agents, are thought to be particularly useful for reducing smoking and other drug use in schizophrenia (Green *et al.* 2007). All patients in this study were medicated with clozapine and although dose was not correlated with attentional bias, clozapine has been associated with reductions in tobacco smoking (George *et al.* 1995; McEvoy *et al.* 1995*b*; Chatterton *et al.* 1998, but see de Leon *et al.* 2005). Recently, cannabidiol has emerged as a potential treatment for schizophrenia (Leweke *et al.* 2012) and it may have additional benefits in terms of substance use because of its relationship with attentional bias (Morgan *et al.* 2010) and tobacco smoking (Morgan *et al.* 2013). Further research into the mechanisms responsible for antipsychotic and anti-addictive effects of current and future drugs should be a key priority, given that the majority of people diagnosed with schizophrenia use tobacco and other drugs of abuse (Awad, 2012).

This study had three main limitations. First, the patients were all medicated with clozapine and so future studies should aim to replicate these findings in different treatment groups. Second, attentional bias was measured using a modified Stroop task with neutral and smoking-related items. Future studies should extend these initial findings using other tasks and additional conditions (e.g. affective words, to demonstrate the specificity of interference to smoking cues) and functional magnetic resonance imaging (fMRI) techniques (Luijten *et al.* 2011) to determine their neural correlates. Nevertheless, the correlation between objective exposure to tobacco (CO) and task performance is consistent with previous findings (Vollstädt-Klein *et al.* 2011), and although the causal direction of this effect is not clear, it does provide some validation of the task. Third, the patient group had lower estimated verbal IQ and higher nicotine dependence scores than controls, and we did not record drug use other than nicotine and clozapine. However, NART and FTND scores did not correlate with the other outcome measures, and the groups were remarkably similar on all other demographic and smoking-related variables.

Conclusions

The results of this study indicate that smoking-related attentional bias is positively associated with the severity of delusions in people diagnosed with schizophrenia. These findings offer preliminary evidence that incentive motivational processes underpinning tobacco smoking are associated with aspects of psychotic illness, which may enhance vulnerability to nicotine use in this population.

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Declaration of Interest

None.

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