Smoking prevalence in schizophrenia is significantly elevated relative to other clinical and to non-clinical groups. The cognitive self-medication hypothesis attributes this to the beneficial effects of nicotine on illness-related cognitive deficits. Significant effects of nicotine have been observed on visual spatial working memory (VSWM), sustained attention (Continuous Performance Test — Identical Pairs; CPT-IP) and prepulse inhibition (PPI). It remains unclear whether these neurophysiological and neurocognitive effects of nicotine influence self-reported smoking motivation.

To explore the relationship between nicotine effects on cognition and self-reported smoking motivation in schizophrenia and non-psychiatric control smokers, the impact of smoking abstinence and reinstatement was examined across three cognitive indices (VSWM, CPT-IP, PPI) and compared to self-reported smoking motivation (‘Modified Reasons for Smoking Scale revised to include ‘cognitive motivators’). Cognitive function was assessed after ‘typical’ smoking and overnight abstinence. Schizophrenia smokers (but not controls) demonstrated significantly less error on the VSWM task in the smoking relative to abstinent condition. Control (but not schizophrenia) smokers, showed evidence of CPT-IP improvement in the smoking relative to abstinent condition. The overall profile of smoking motivation was comparable between groups. However, significant relationships between subjective and objective indices of smoking related cognitive change were observed for controls. Differential effects of nicotine on cognition have been hypothesised to influence the pattern and persistence of smoking in schizophrenia. These preliminary findings indicate that evidence for such effects is apparent even in small samples — particularly for VSWM. This is the first study to show that neurocognitive effects of smoking may influence self-reported smoking motivation.

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relative impact of smoking abstinence and re-instatement on three tasks measuring putative endophenotypic markers of schizophrenia (sustained attention, visual spatial working memory and sensory gating). Finally, we explored the relationship between self-reported motivations for smoking (i.e. perceived function of smoking) and objective indices of the physiological impact of nicotine on cognitive functioning.

1. Method

This study consisted of two experimental sessions. A ‘self-report only’ component was also introduced to assess smoking motivation amongst individuals unable or unwilling to participate in experimental sessions. This study was conducted in accordance with the ethical standards (3.10, 8.01, 8.02 and 8.06) of the American Psychological Association. Written, informed consent was obtained from all participants. Study protocol was approved by the University of Newcastle and Hunter New England Human Research Ethics Committees.

1.1. Participants

Twenty-eight smokers (≥ 15 cigarettes per day), 16 outpatients who met DSM-IV criteria (DIP; Castle et al., 2006) for schizophrenia (n = 10) or schizoaffective disorder (n = 6) and 12 community controls without a personal history of psychosis/major affective disorders (DIP; Castle et al., 2006) participated in experimental sessions. Exclusion criteria included neurological condition (e.g. stroke, epilepsy), significant head injury/trauma and evidence of alcohol or illicit substance dependence within the last six months. An additional 71 smokers, 43 outpatients with schizophrenia/schizoaffective disorder and 28 non-psychiatric controls provided self-report data only.

1.2. General procedures

Experimental participants attended two morning appointments (approximately one week apart), one after abstaining from nicotine from at least one week apart), one after abstaining from nicotine from at least 1 week (e.g. Adler et al., 1993; ‘abstinent’), the other in the context of usual smoking behaviour (‘smoking’). The order of cognitive assessment was randomly allocated from one of six testing orders, generated using a Latin square design. Appointment order (abstinent first vs. second) was alternated within each of the six testing orders. Self-reported smoking motivation was assessed during the ‘smoking’ appointment. Self-report only participants completed a questionnaire pack assessing demographics, smoking history, self-reported dependence and smoking motivation.

1.3. Measures and instruments

1.3.1. Cigarette and substance use measures

Self-reported smoking status (abstinent vs. smoking) was verified at the beginning of experimental appointments with single breath, expired CO using a Bedfont Micro Smokerlyzer (Air-met Scientific). For the abstinent session a CO reading of ≤12 ppm (e.g. Kumari and Gray, 1999) was required. Withdrawal symptoms were assessed using the Wisconsin Smoking Withdrawal Scale (WSWS; Welsch et al., 1999). Self-reported nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence (FTND; Steinberg et al., 2005).

1.4. Smoking motivation

Self-reported smoking motivation was assessed using a revised version of the Modified Reasons for Smoking Scale (MRSS; Tate et al., 1994). Thirteen items from the Situation × Trait Adaptive Response Smoking Motivation Questionnaire (STAR-SMQ; Gilbert et al., 2000) were combined with the MRSS into a single, comprehensive measure of self-reported smoking motivations (MRSS-Revised). Participants were required to rate each item using a five-point Likert scale (1 = Never, 5 = Always; Forchuk et al., 2002).

1.5. Cognitive assessment

1.5.1. VSWM

VSWM was assessed using a computerized task designed in accordance with published specifications (George et al., 2006). Participants moved a cursor to the location of a previously observed dot with performance indexed by the average distance (error, in cm) between the cursor and the actual location of target presentation, averaged across 16 trials. Higher scores indicate poorer performance.

1.5.2. Sustained attention

Sustained attention was assessed using the Continuous Performance Task — Identical Pairs version (CPT-IP: number trial only; Michie et al., 2000). Outcome measures included hits (correct responses to targets), false alarms (catch and filler trials), response time (ms) and discrimination (d; Comblatt et al., 1988), calculated for blocks 1 & 2 of the task separately to provide sensitivity to changes over the testing period.

1.5.3. PPI

The PPI paradigm was programmed according to published specifications (George et al., 2006). Auditory stimuli were presented binaurally over headphones. Acoustic startle response was measured via eye-blinks using electromyographic activity (EMG) collected using Scan 4.3 (Neuroscan Inc, Biomedics). EMG activity was acquired continuously (A/D rate of 250 Hz) and filtered with a 0.1–30 Hz bandpass filter and 5-Hz notch filter. EMG data were inspected to determine responsiveness of participants to the startle alone stimulus. Participants were classified as ‘acoustic startlers’ if they demonstrated a mean startle response of ≥ 25 μV in the smoking session (George et al., 2006), with this criterion applied to the mean of the startle alone trial across the first third blocks only (where habituation effects are weakest; Braff et al., 1992) resulting in the rejection of one schizophrenia participant.

Spontaneous and voluntary eye blinks in these data sets were then excluded according to previously published criteria (Braff et al., 1992), with 12.5% of trials in controls and 13.89% of trials in schizophrenia participants discarded (comparable to George et al., 2006). Peak amplitude, peak latency and mean amplitude (over 50–200 ms) values were extracted for analysis. PPI was defined as the difference in startle magnitude (as a percentage) between pulse trials preceded by a prepulse and pulse alone trials [1 − (pp/pp)×100; where pp represents the mean amplitude to pulse trials preceded by a prepulse, and represents the mean amplitude over pulse alone trials].

2. Results

Statistical analysis was performed using SPSS v 16.0. An alpha level of .05 was used for all statistical tests.

2.1. Demographic and clinical characteristics

Tables 1 and 2 display results of independent samples t-tests or χ² analyses comparing schizophrenia versus control participants on demographic, clinical and smoking variables. Schizophrenia participants demonstrated lower estimated full scale IQ (although within average limits; Table 1) and higher self-reported nicotine dependence (Table 2).

2.2. Cognitive assessment

Due to small group numbers analysis of all cognitive data was restricted to within-subjects comparisons.

2.2.1. VSWM

Paired-samples t-tests demonstrated that schizophrenia (t(15) = 2.93, p = .01, Cohen’s d = 0.6], but not control (p = .81) smokers demonstrated significantly better performance during typical smoking, relative to short-term (i.e. overnight) abstinence (Fig. 1).

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### Table 1
Demographic and clinical characteristics for experimental (EXP) and self-report participants (S-R)².

|                        | Schizophrenia Smokers | Control Smokers | p-value |
|------------------------|-----------------------|-----------------|---------|
|                        | EXP (n = 16)          | S-R (n = 43)    |         |
| Recruitment Source     |                       |                 |         |
| CTNMHI Volunteer Database | 50%                  | 63%             |         |
| ASRB Volunteer Database | 19%                  | 22%             |         |
| HMRI Volunteer Database | –                    | –               |         |
| Media                  | 19%                  | –               |         |
| Flyers                 | 12%                  | 9%              |         |
| Schizophrenia Fellowship | –                   | 6%              |         |
| Age                    | 43 (10.8)            | 43 (9.78)       |         |
| Gender (% Male)        | 56.3                 | 48.8            |         |
| WTAR Estimated Full-Scale IQ^b | 99.1 (7.2)       | 104.3 (5.7)     | .05     |
| Self-reported age of illness onset^b | 21.87 (6.09)       | 19.08 (4.22)    |         |
| Duration               | 21.13 (9.19)         | 24.97 (9.67)    |         |
| Antipsychotic class^c  |                      |                 |         |
| Atypical               | 12                   | 35              |         |
| Typical                | 2                    | 9               |         |
| CPZ equivalents (mg/day)^b | 363.62 (293.66)     | 612.05 (466.98) | .03     |

Note: ASRB = Australian Schizophrenia Research Bank; CTNMHI = Centre for Translational Neuroscience and Mental Health Research; CPZ = chlorpromazine; HMRI = Hunter Medical Research Institute; WTAR = Weschler Test of Adult Reading.
² Values are expressed as a percentage of the group unless otherwise specified.
³ Values are expressed as mean (SD).
† Values are expressed as the total number of participants.
* Significant at p < .05.

### Table 2
Smoking variables for experimental and self-report participants^a.

|                        | Schizophrenia Smokers | Control Smokers | p-value |
|------------------------|-----------------------|-----------------|---------|
|                        | EXP (n = 16)          | S-R (n = 43)    |         |
| Smoking onset (1st full cigarette) | 12.9 (4.7)             | 13.6 (3.8)     | .77     |
| Age of daily smoking onset | 16.6 (5.3)            | 17 (4.5)       | .53     |
| Years since onset of daily smoking | 26.4 (10.2)          | 25.9 (10.5)    | .13     |
| Smoking behaviour in last 12 months^b | 12.5               | 17.9            | .18     |
| Changed to lower nicotine cigarette | 18.8              | 22.1            | .79     |
| Reduced average daily cigarettes | 31.3             | 48.7            | .04*    |
| Smoking behaviour unchanged | 25                | 25              | .92     |
| Lifetime number of quit attempts | 5.8 (6.8)              | 8.9 (13.6)     | .24     |
| Longest period of abstinence (weeks)^b | 12.5              | 25              | .09     |
| FTND Total Score^a | 6.8 (1.8)             | 7.2 (1.7)       | .003**  |
| FTND Dependence Category^a | Mild               | 25              | .005**  |
| High                   | 37.5                 | 31.3            | .25     |
| Very High              | 32.0                 | 42.1            | .15     |

Note: FTND = Fagerström Test for Nicotine Dependence (self-report inventory).
^a Values are expressed as mean (SD) unless otherwise specified.
^b Values are expressed as a percentage of the group.
* Significant at p < .05.
** Significant at p < .01.
The discrimination ability of schizophrenia smokers appears to marginally improve between blocks one and two, irrespective of smoking status. However, RMANOVA's performed on the DL data of schizophrenia participants did not reach significance (all $p's > .08$).

### 2.2.3. PPI

PPI across the three prepulse intervals (as a function of smoke status) appears in Fig. 3. RMANOVA's revealed no significant effect of smoke status for either group (all $p's > .19$). A significant effect of trial type was detected for control ($\epsilon = 0.71, F(2,20) = 19.48, p < .001$), but not schizophrenia participants. In controls, PPI was significantly larger in the 60 ms ($t(10) = 5.64, p < .001$; Cohen's $d = 1.00$) and 120 ms ($t(10) = 7.65, p < .001$; Cohen's $d = 1.09$) conditions relative to the 30 ms condition (no difference was detected between the 60 ms and 120 ms conditions, $p = .54$).

### 2.3. MRSS-R

Ninety-eight participants (schizophrenia = 58, control = 40) returned the MRSS-R (one from the schizophrenia group was excluded due to excessive missing data). Mean MRSS-R subscale scores were entered into a 2 (Group: schizophrenia vs. control) × 8 (Motive: cognitive vs. automatic vs. addictive vs. stimulation vs. sedative vs. indulgent vs. sensorimotor manipulation) RMANOVA, with group as a between-subjects factor and motive as a within-subjects factor. Separate ANCOVA's and Spearman Rank correlations were conducted to determine whether self-reported nicotine dependence (as indexed by FTND scores) influenced self-reported motivation to smoke.

Cognitive motives represent an ‘occasional’ reason for smoking in both groups (Fig. 4a). An RMANOVA conducted on the MRSS-R data produced a significant main effect of motive ($\epsilon = .83; F(7,672) = 71.09, p < .001$) but no motive × group interaction ($p = .26$) or main effect of group ($p = .11$).
Cognitive motives continued to represent an ‘occasional’ reason for smoking in both groups after co-varying for the effect of FTND (Fig. 4b). FTND was a significant co-variate \( F(1,95) = 23.94, p < .001 \). Entering FTND as a covariate in an RM ANCOVA produced a significant main effect of motive \( \varepsilon = .85; F(7,665) = 5.8, p < .001 \) along with a significant motive × group interaction \( \varepsilon = .85; F(7,665) = 2.8, p = .01 \), with stronger endorsement of sedative motivators amongst controls \( t(96) = 3.11, p < .01 \). The main effect of group remained non-significant \( (p = .67) \). Correlations between FTND and MRSS-R subscale scores are presented at the end of this section in Table 3.

2.4. Relationship between cognitive function and self-reported smoking motivation

Difference scores were calculated for each of the primary cognitive performance indices (Smoking minus Abstinent). Analyses were conducted separately for each group. Significant correlations were detected between self-reported cognitive smoking motivation and CPT-IP measures only and in controls only.

Amongst controls, there was a significant positive correlation between block two hits and the ‘cognitive’ \( (r = .67, p = .02) \) motivator (Fig. 5). That is, stronger endorsement of ‘cognitive’ items was associated with a larger smoking-related increase in block two hit rate.

3. Discussion

To our knowledge, this is the first study to attempt a multi-level evaluation of subjective and objective cognitive effects of nicotine. Deficits within the three cognitive domains assessed are suspected endophenotypic markers for schizophrenia, and as such, are particularly pertinent to understanding the relationship between nicotine and cognition within this illness. Consistent with prior research (Sacco et al., 2005; Smith et al., 2006), smoking vs abstinence had a clear and significant impact on the VSWM function of smokers with schizophrenia. Relative to overnight abstinence, VSWM performance in the smoking appointment was characterised by significantly smaller error. In contrast, the VSWM performance of control smokers remained consistent across appointments. This study provides further support for the sensitivity of VSWM (dys)function to manipulation of nicotine use in smokers with schizophrenia.

Despite apparent impairments in CPT-IP performance, contrary to prediction, sustained attention in schizophrenia smokers was unaffected by the smoking/abstinence manipulation. Conversely, amongst controls, both hits and discrimination ability were significantly higher in the smoking relative to abstinent appointment. The absence of smoking related change in our schizophrenia group is inconsistent with existing evidence (Dépatie et al., 2002; Levin et al., 1996; Sacco et al., 2005; Smith et al., 2006). A notable difference between our study and Dépatie...
smokers who reported stronger cognitive motivations for smoking and furthermore, that smokers with schizophrenia would offer a higher level endorsement of cognitive motivators for smoking and furthermore, that smokers with schizophrenia would offer a higher level endorsement of cognitive motives in schizophrenia relative to non-psychiatric smokers. According to the Primary Addiction Hypothesis (Chambers et al., 2001), addiction is conceived to be a primary symptom of the schizophrenia syndrome, due to fundamental commonalities in the neurobiology of schizophrenia and addiction (Chambers et al., 2001). Therefore, our self-report data could be interpreted as evidence for smoking in schizophrenia as a biologically driven process (addiction vulnerability) that is independent from subjective awareness.

However, we did find an interesting relationship between cognitive motivators and smoking related change in the sustained attention performance of controls. It is noteworthy that the cognitive task with which self-reported cognitive motives did correlate could be argued to be the most general and most easily definable in lay terms — that is, sustained attention. This finding could be interpreted as having dual implications: that if we wish to assess correlations between motivation and cognition we require tasks that measure general abilities that map well to lay-description of cognitive effects; and that if we wish to better understand the pathways by which nicotine affects cognition, we may require more specific tasks where the contributions of various cognitive operations can be delineated.

The current study is limited by a small sample size, meaning that we were restricted to within subjects comparisons on cognitive measures and correlational analyses were underpowered. Although the reporting of within subjects effects of nicotine versus abstinence in prior research does not enable us to calculate power for PPI and VSWM, the effect size derived from published findings for CPT-IP (Cohen’s dz = 0.89; Dépatie et al., 2002) supports the expectation for relatively ‘large’ effects of nicotine (based on Cohen, 1988) on this task. For schizophrenia participants, post-hoc power analysis using Gpower (α = .05, two-tailed, dependent means; Faul et al., 2007) demonstrated adequate statistical power (.80) for detecting moderate to large effects (≥.75) of nicotine on CPT-IP performance.

If we had not observed any significant effects then one might reasonably question that the significance of the results might be limited by sample size. However, what we did see was a significant effect on VSWM in patients despite no significant effect on CPT-IP and PPI. This result then replicates published findings in an independent laboratory and adds to the evidence that this measure appears particularly sensitive to nicotine effects in schizophrenia. Moreover, unlike several prior investigations (e.g. George et al., 2006; Olincy et al., 2006; Sacco et al., 2005) we did not experimentally manipulate the nicotinic agonist/antagonist administration. It was therefore possible to counterbalance the smoking and abstinence appointment and thereby reduce the contribution of any practice or order effects. This design distinguishes the current study from prior research in the area (e.g. Levin et al., 1996; Sacco et al., 2005; George et al., 2006; Postma et al., 2006) and should be

### Table 3

Non-parametric correlations between self-reported nicotine dependence (FTND) and MRSS-R subscale scores for schizophrenia and control smokers.

| Factor                | Schizophrenia | Control |
|-----------------------|---------------|---------|
|                       | r             | p-value | r      | p-value |
| Cognitive             | .230          | .082    | .325   | .041*** |
| Automatic             | .216          | .103    | .499   | .001*** |
| Addictive             | .397          | .0028   | .549   | <.001*** |
| Stimulation           | .336          | .010    | .309   | .052    |
| Sedative              | .384          | .003*** | .477   | .002*** |
| Social                | .451          | <.001***| .122   | .455    |
| Indulgent             | .171          | .200    | −.084  | .607    |
| Sensorimotor Manipulation | .171        | .198    | −.037  | .822    |

* Significant at p < .05.
** Significant at p < .01.

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et al. (2002) is the route of nicotine administration (smoking vs. transdermal nicotine patch). Nicotine nasal spray demonstrates a similar pharmacokinetic profile to smoking (Zevin et al., 1998), and consistent with our findings, there is some evidence that CPT-IP performance of smokers with schizophrenia is unaffected by nicotine nasal spray (Sherr et al., 2002). Furthermore, Levin et al. (1996) and Sacco et al. (2005) both used Conner’s CPT. In Conner’s CPT, selective attention and response inhibition are more strongly emphasised (Dépatie et al., 2002); whereas CPT-IP (used in the current study) is a more sensitive assessment of sustained attention and working memory processes (Dépatie et al., 2002; Michie et al., 2000). One potential implication is that, in schizophrenia, the neural networks mediating selective attention and response inhibition (i.e. Conner’s CPT) may demonstrate a differential response to nicotine, relative to sustained attention and working memory (i.e. CPT-IP). Comparing the effect of nicotine across different CPT task versions in a single study may help to clarify apparent discrepancies in the literature.

Contrary to expectation, PPI in smokers with schizophrenia was unaffected by smoking status. In light of existing evidence (e.g. Adler et al., 1993; George et al., 2006; Olincy et al., 2006; Woznica et al., 2009) it would be premature to interpret the current findings as evidence for an absence of effect. The observed discrepancy between the current findings and existing evidence may result from differences in the proximity between smoking and assessment (due to counterbalancing in the current study) and the use of left, relative to right eye EMG. For example, Cadenhead et al. (2000) demonstrated that, as a group, smokers exhibited higher PPI for right but not left eye EMG (Cadenhead et al., 2000). The relative effect of nicotine on right vs. left eye EMG represents an interesting area for future research. Utilisation of bilateral recording procedures may help to more clearly elucidate whether smoking related effects in schizophrenia demonstrate evidence of hemispheric asymmetry.

In summary, we predicted that smoking related change on three putative endophenotypic markers would be strongest for smokers with schizophrenia. This hypothesis was supported by evidence from a computerised version of the VSWM task, but not CPT-IP or PPI. Importantly, change in VSWM function was specific to the schizophrenia group and occurred irrespective of the factors that may have contributed to null effects on CPT-IP (e.g. nicotine dose) and PPI (e.g. temporal proximity to nicotine). Evidently, VSWM function may be especially sensitive to smoking related performance change in schizophrenia.

Informed by the cognitive self-medication hypothesis, we predicted that smokers with schizophrenia would offer a higher level endorsement of cognitive motivators for smoking and furthermore, that smokers who reported stronger cognitive motivations for smoking would also demonstrate a stronger impact of nicotine on cognitive functioning. Our data suggest that, on the measures used here, there is no inflation of cognitive motives in schizophrenia relative to non-psychiatric smokers. According to the Primary Addiction Hypothesis (Chambers et al., 2001), addiction is conceived to be a primary symptom of the schizophrenia syndrome, due to fundamental commonalities in the neurobiology of schizophrenia and addiction (Chambers et al., 2001). Therefore, our self-report data could be interpreted as evidence for smoking in schizophrenia as a biologically driven process (addiction vulnerability) that is independent from subjective awareness.

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![Fig. 5. Scattergram of difference scores for CPT-IP hits (block two) in relation to self-reported 'cognitive' smoking motivation scores in non-psychiatric smokers.](image-url)"
considered in interpreting differences in smoking related effects in the current study, relative to prior research.

It is also worth noting that the abstinence criterion adopted in the current study (< 12 ppm) is consistent with some (e.g. Kumari et al., 1996; Kumari and Gray, 1999), but higher than others (e.g. Sacco et al., 2005; Smith et al., 2002). Given that the mean CO level for both participant groups during the abstinence appointment (control = 8.78; schizophrenia = 8.75) is comparable to studies adopting the more stringent criterion (e.g. Sacco et al., 2005), surreptitious smoking is unlikely to have contributed to our findings. However, future research should consider employing more definitive methods for verifying abstinence (e.g. plasma nicotine levels).

In summary, task choice in this study was based on those for which existing data supported nicotine effects in schizophrenia (see Sacco et al., 2004). Whether these are the most sensitive indices and indeed the specific components of task performance facilitated by nicotine has yet to be determined. Developing sensitive indices of nicotine-induced cognitive enhancement is an important precursor to attempts to link changes in performance on these tasks to self-report motives, as is the challenge of developing more intuitive descriptions of how ability changes might manifest in everyday life. Findings from the current study highlight several methodological considerations for this type of research and promising avenues for future study. Improved understanding of the subjective, neurophysiological and neurocognitive effects of nicotine represents an important step for developing improved smoking cessation strategies.

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effects of nicotine represents an important step for developing the understanding of the subjective, neurophysiological and neurocognitive type of research and promising avenues for future study. Improved understanding of the subjective, neurophysiological and neurocognitive effects of nicotine represents an important step for developing improved smoking cessation strategies.

Contributors

All authors contributed and have approved the final manuscript.

Conflict of interest

No conflict of interest to declare.

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