

Early nicotine withdrawal and transdermal nicotine effects on neurocognitive performance in schizophrenia

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Abstract

As cigarette smoking prevalence rates approach 90% in schizophrenia, an important emerging question is the role of nicotine in the disease-related disturbance in cognition. We therefore tested a total of 38 male cigarette smokers (22 schizophrenia, 16 normal control), matched on nicotine dependence, on the Attention Network Test (ANT) at three nicotine conditions (baseline, 8 h overnight withdrawal, 3 h 21 mg nicotine patch). The results indicated that the groups did not differ in performance on either of three ANT measures (alertness, orienting, and executive) across baseline, patch, and withdrawal conditions. However, in comparison to the controls, the participants with schizophrenia showed faster ANT reaction time (RT) for the nicotine patch in relation to the baseline condition. In comparison to controls, the participants with schizophrenia also showed reduced ANT accuracy at withdrawal but not at patch condition. These results suggest that overall processing speed and accuracy are affected differently by nicotine levels in participants with schizophrenia, with evidence supporting greater impairment from withdrawal and greater improvement from nicotine administration.

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1. Introduction

Prevalence rates of cigarette use in schizophrenia approach 70–90% (Dalack et al., 1998), and the reasons for increased use are not well understood (McCloughen, 2003). Smokers with schizophrenia have elevated rates

of lung cancer (Lichtermann et al., 2001), cardiovascular disease (Osby et al., 2000), tardive dyskinesia (Chong et al., 2003) and polydipsia (de Leon et al., 2002). Biological abnormalities of nicotinic acetylcholine receptors are also established in schizophrenia including $\alpha 4\beta 2$ (hippocampus, Freedman et al., 1995; striatum, Durany et al., 2000) and $\alpha 7$ subunits (hippocampus, Leonard et al., 1998, 2000).

Smoking may ameliorate many well described cognitive deficits in schizophrenia. Nicotine is known to enhance cognition (Kumari et al., 2003), including attention and memory (George et al., 2001; Levin et al.,

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1996), which are impaired in schizophrenia (Fioravanti et al., 2005). Previous studies in schizophrenia report improved reaction time with nicotine spray (Smith et al., 2006) but impaired accuracy at withdrawal with a return to baseline following smoking reinstatement (Sacco et al., 2005).

The Attention Network Test (ANT), a novel means of evaluating attention functioning, has received empirical support in the literature (Fan et al., 2002, 2005). In combining flanker (Eriksen and Eriksen, 1974) and cue reaction time (Posner, 1980) paradigms, the ANT provides a measure of the efficiency of three independent networks of attention, referred to as alerting, orienting, and executive (Fan et al., 2002). Each network is associated with differential activation of particular networks of neuroanatomical regions (Fan et al., 2002, 2005). The alerting network, which uses warning signals to provide for faster information processing, is associated with norepinephrine frontal and parietal circuits within the right hemisphere (Coull et al., 1996; Marrocco et al., 1994). The orienting network, which uses directional warning signals to facilitate stimuli location detection, is associated with thalamic, frontal and superior parietal regions (Corbetta et al., 2000; Rafal and Posner, 1987). The executive network, which provides resolution of conflict, processing of novel stimuli and error detection, is associated with the anterior cingulate cortex and lateral prefrontal cortex (Bush et al., 2000; Posner and DiGirolamo, 1998).

The use of the ANT as a cognitive measure has been reported in schizophrenia (Nestor et al., 2007; Gooding et al., 2006; Wang et al., 2005). It has been also used to assess nicotine impact. Following overnight abstinence in cigarette smokers, 21 mg nicotine patch had no effect on attention networks but both nicotine and denicotinized cigarettes improved alerting attention (Kleykamp et al., 2007). In schizophrenia, attention studies using the ANT are inconsistent. Wang et al. (2005) report more impaired orienting and executive network function in schizophrenia compared to a control group. In contrast, Nestor et al. (2007) reported reduced alerting network function, which was associated with a smaller white matter fiber tract in the cingulum bundle. Gooding et al. (2006) suggest a specificity of executive attention dysfunction in schizophrenia as well as poorer reaction time and accuracy rates to controls. Despite the variability, the ANT is a useful method of attention assessment in schizophrenia.

We examined the effects of nicotine levels on attention networks and performance functioning in schizophrenia. Using a design that included repeated administration of the ANT at baseline, post-overnight

withdrawal and post-transdermal nicotine patch, we planned to understand how nicotine might impact attention networks and performance measures (i.e., RT and accuracy). We predicted that persons with schizophrenia would demonstrate greater impairment in attention network function in comparison to control participants. Nicotine level was expected to predict outcomes (transdermal patch > baseline > withdrawal), with a schizophrenia diagnosis associated with greater impairment. In addition, we analyzed performance measures to better understand how they are affected by nicotine levels manipulations.

2. Materials and method

2.1. Participants

Participants, 18–60 years old, with DSM-IV (SCID-P; First et al., 1997) schizophrenia or schizoaffective disorder were recruited from the VA Boston Healthcare System. Control participants, 18–60 years old, were recruited from the community. Exclusion criteria for schizophrenia participants included alcohol/drug abuse (past year) and dependency (past five years), allergy/

Table 1
Demographic and clinical characteristics of groups

Variable	Schizophrenia (<i>n</i> =22), <i>M</i> (SD)	Control (<i>n</i> =16), <i>M</i> (SD)
Age, years	47.59 (8.06)	42.31 (11.18)
Education, years	12.45 (1.82)	14.25 (1.65)**
Height, in.	70.32 (3.76)	71.13 (2.50)
Weight, lb	206.27 (45.75)	184.31 (29.16)
Body mass index	29.55 (7.27)	25.59 (3.73)*
Age of illness onset, years [^]	22.11 (3.83)	
Illness duration, years [^]	25.79 (8.14)	
WAIS-III FSIQ	88.53 (11.86)	
PANSS positive scale [^]	18.63 (8.56)	
PANSS negative scale [^]	20.84 (8.21)	
PANSS general psychopathology scale [^]	36.68 (14.33)	
PANSS total score [^]	76.16 (26.44)	
SAPS total score [^]	8.47 (3.06)	
SANS total score [^]	10.00 (6.32)	
Time 1 CPZ equivalent (mg/day)	640.91 (531.54)	
Time 2 CPZ equivalent (mg/day)	627.78 (589.67)	

p*<.05, *p*<.01, [^]*n*=19.

CPZ (Chlorpromazine); WAIS-III (Wechsler Adult Intelligence Scale — III; Wechsler, 1997); PANSS (Positive and Negative Syndrome Scale; Kay et al., 1987); SAPS (Scale for the Assessment of Positive Symptoms; Andreasen, 1984); SANS (Scale for the Assessment of Negative Symptoms; Andreasen, 1981).

hypersensitivity to adhesives, current smoking cessation treatment, history of seizure disorder, neurological illnesses, or severe head injury. Additional exclusion criteria for controls included personal or 1st degree relative history of diagnosed Axis I disorders. All procedures were approved by institutional review boards at the VA Boston Health Care System, Harvard Medical School and University of Massachusetts Boston.

Forty-five cigarette smokers were recruited (27 schizophrenia, 18 control). Twenty-two schizophrenia and 16 control participants completed all testing conditions; two participants with schizophrenia were unable to abstain from smoking overnight and five (3 schizophrenia, 2 normal control) lost interest. Consistent with the literature, the schizophrenia group ($M=12.45$, $SD=1.82$) demonstrated fewer completed years of education than controls ($M=14.25$, $SD=1.65$), $t_{36}=3.12$, $p<.01$. Clinical ratings were completed for current negative (SANS; Andreasen, 1981), positive (SAPS; Andreasen, 1984), and overall (PANSS; Kay et al., 1987) symptoms in the patient sample (see Table 1). Full-scale WAIS-III scores, collected as part of an earlier study, are also presented for the participants with schizophrenia in Table 1. These scores were not collected from normal control participants.

2.2. Measures and instruments

2.2.1. Fagerström Test for Nicotine Dependence (FTND)

The FTND is a 6-item self-report questionnaire of smoking-related nicotine dependence (Heatherton et al.,

1991). Participants report information on timing and importance of cigarette use with total scores ranging from 0 to 10. A score of seven or greater is considered highly physically dependent on nicotine.

2.2.2. Attention Network Test (ANT)

The ANT is a 20-minute visual decision task consisting of a central target arrowhead, (e.g., →) flanked by either four arrowheads (e.g., → → → → →) or dashes (— — → — —), presented in black on a light-gray background (see Fan et al., 2002; Fig. 1). Arrowhead configurations included both leftward and rightward orientations. Flankers were of similar (congruent) or opposite (incongruent) direction or black lines (neutral). Arrowhead stimuli were presented either above or below a center fixation cross (+). Participants were seated 65 cm from a laptop computer screen and the paradigm was administered using E-Prime software. Participants were asked to report the direction of the central arrowhead as quickly and as accurately as possible using two mouse buttons.

Trials included a warning cue (*) condition and target type configuration. The warning cue was presented centrally (center cue), above or below the fixation cross (spatial cue), above and below the fixation cross (double cue) or not at all (no cue). Twenty four practice trials were first provided and included visually-displayed reaction time and cumulative accuracy feedback. A total of 96 test trials were administered (4 warning cue conditions × 2 target arrowhead locations × 2 target arrowhead directions × 3 distractor stimuli conditions × 2 repetitions).

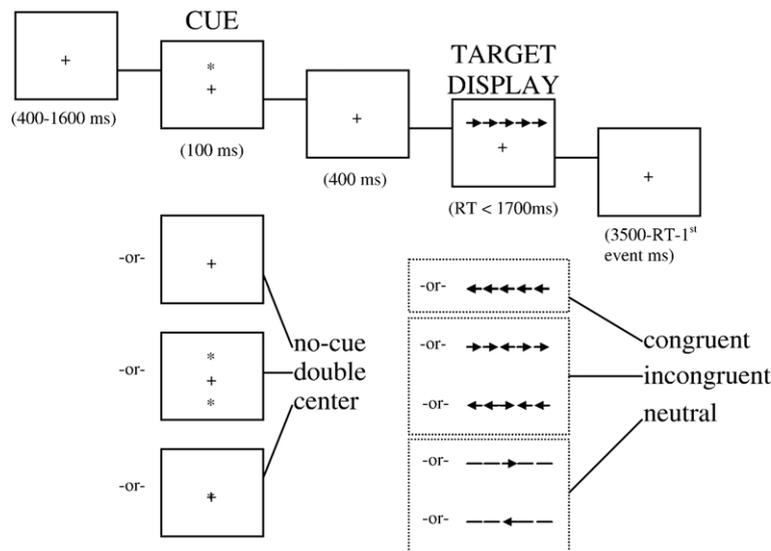


Fig. 1. ANT procedure.

Alertness was calculated by subtracting the median RTs to the target during double-cue from the no-cue condition; orienting was calculated by subtracting the median RTs to targets preceded by the spatial cue from the median RTs in the center cue condition; executive attention network function was calculated by subtracting the median RTs of congruent from incongruent distractor conditions. Overall mean RT and accuracy (% correct) were calculated.

Repeated administration of the ANT is considered to be reliable, without evidence of practice effects on attention networks (Fan et al., 2002). Participants do not memorize specific stimuli or make responses that may be affected by the novelty of the stimuli. Also, a 5-minute practice session is designed to allow all participants at each session to become familiar with the task. Therefore, practice effects on this task are not considered to interfere with the results.

2.2.3. Transdermal nicotine patch

A 21 mg Nicoderm® CQ transdermal nicotine patch delivered a controlled level of nicotine to participants. This system is safe and effective for the study of nicotine in smokers with (Chou et al., 2004; Levin et al., 1996) and without (Lawrence et al., 2002) schizophrenia. The nicotine patch, instead of smoking reinstatement, was selected in order to control for the amount of nicotine delivered. Smoking reinstatement is likely to be different according to both individual smoking characteristics and group membership (Tidey et al., 2005). Participants were monitored for adverse side effects of the nicotine patch and concomitant use of cigarettes during patch administration was forbidden (Fant et al., 1999).

2.2.4. Saliva collection and analysis

Saliva is a valid and reliable method of measuring nicotine levels (Rose et al., 1993). Unstimulated saliva samples were provided by participants at each assessment. Samples were transferred into 2 ml cryogenic vials and stored at -40°C before shipment for nicotine analysis (Labstat International Inc.) using gas chromatography with thermionic specific detection (Dhar, 2004). Nicotine levels were reported in nanograms/milliliter (ng/ml).

2.3. Experimental procedure

All recruited participants first provided informed consent. On the first day, participants were administered the FTND, baseline ANT (no smoking for 1 h) and provided a saliva sample. Within a week, participants

returned to complete early withdrawal and nicotine patch assessments. For early withdrawal, participants abstained from smoking cigarettes overnight (8 h). If abstinence was accomplished, participants completed the ANT and gave a saliva sample. If participants were not able to abstain, testing was rescheduled. Following the early withdrawal ANT and saliva assessment, the 21 mg Nicoderm CQ patch was applied. During a 3-hour patch administration period, participants viewed an entertainment videotape in the laboratory. Participants then completed the ANT and gave a saliva sample. Following testing, the nicotine patch was removed and psychoeducation on smoking effects and cessation programs was provided.

3. Results

3.1. Nicotine analyses

Three participants (2 control, 1 schizophrenia) were removed from analyses given abnormally high nicotine levels (z -score >2.50 ; Stevens, 1999). These abnormal levels were found at baseline (1 control), withdrawal (1 control, 1 schizophrenia) and nicotine patch (1 control). One control participant had elevated nicotine levels at both baseline and nicotine patch assessments. Analyses were completed with 21 participants with schizophrenia and 14 controls.

A 2×3 mixed-model ANOVA with one between-subject factor of group (schizophrenia, control) and one within-subject factor of session (baseline, early withdrawal, nicotine) was computed for salivary nicotine levels (Table 2). Significant main effects of group, $F(1,32)=7.00$, $p<.05$ and session, $F(2,31)=13.00$, $p<.001$, were reported but not the interaction, $F>1$. Overall, increased nicotine levels were reported in schizophrenia ($M=253.00$, $SE=28.37$) compared to controls ($M=127.65$, $SE=36.10$). Across groups, withdrawal nicotine levels ($M=88.90$, $SE=28.69$) were reduced compared to baseline ($M=225.20$, $SE=45.97$) and patch ($M=290.32$, $SE=31.03$) assessments. Post-hoc

Table 2
Saliva nicotine levels (ng/ml) according to condition

	Schizophrenia ($n=20$), M (SE)	Control ($n=14$), M (SE)
Baseline (no smoking: 1 h)	285.66 (49.11)	137.76 (86.91)
Early withdrawal (no smoking: 8 h)	141.06 (46.06)	14.85 (3.98)
Nicotine patch (nicotine: 3 h)	332.30 (41.47)	230.34 (41.26)

analyses revealed greater nicotine levels in schizophrenia than controls at early withdrawal, $t_{33}=2.74$, $p<.05$.

3.2. Self-reported smoking behavior

Nicotine dependence ratings (FTND) were similar in schizophrenia ($M=5.90$, $SD=1.81$) and controls ($M=4.71$, $SD=2.79$). However, item analysis using chi-square statistics indicated that 71.4% of participants with schizophrenia reported the first cigarette of the day as more difficult to give up compared to 35.7% of controls, $\chi^2(1, N=35)=4.38$, $p<.05$. Additional chi-square item analyses were not significant (Table 3).

3.3. Attention Network Test

3.3.1. Measures of alerting, orienting, and executive attention networks

A $2 \times 3 \times 3$ repeated-measures ANOVA with group (schizophrenia, control) as the between-subject factor along with network type (alerting, orienting, executive) and condition (baseline, withdrawal, patch) as within-subject factors was computed. Performance measures of network types were calculated using RT difference scores as described in Section 2.2.2. Analyses revealed a significant main effect of network type, $F(2,32)=20.72$, $p<.001$, and the interaction between network and condition, $F(2,32)=3.21$, $p<.05$. Executive network function (113.2 ms) was slower than either alerting (28.4 ms) or orienting (55.3 ms) network measures in both groups. Also, for both groups, faster executive function occurred during nicotine patch (125.1 ms) in comparison to baseline (102.0 ms), $t_{34}=2.52$, $p<.05$.

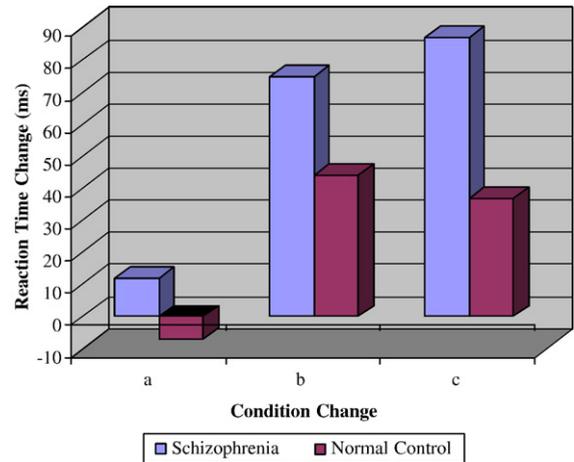


Fig. 2. Reaction time change score calculations between nicotine conditions including (a) baseline — withdrawal, (b) withdrawal — nicotine patch and (c) baseline — nicotine patch.

3.3.2. Reaction time

A 2×3 mixed-model ANOVA revealed that participants with schizophrenia ($M=744.7$ ms) had overall slower RT than controls ($M=596.1$ ms), $F(1,33)=10.78$, $p<.01$. Participants with schizophrenia showed slower RT than controls at baseline ($t_{33}=3.26$, $p<.01$), withdrawal ($t_{33}=3.18$, $p<.01$), and nicotine patch ($t_{33}=2.86$, $p<.01$). Across groups, RT following nicotine patch ($M=629.6$ ms) was fastest compared with baseline ($M=691.9$ ms) and withdrawal ($M=689.4$ ms) conditions, $F(2,32)=20.25$, $p<.001$. A one-way between-group ANOVA for RT change between nicotine conditions indicated that participants with schizophrenia

Table 3
Fagerström test for nicotine dependence (FTND) item percentage scores for each group

Question		Schizophrenia ($n=21$)	Control ($n=14$)
1. How soon after you wake up do you smoke your first cigarette?	61+ min	4.8	14.3
	31–60 min	4.8	7.1
	6–30 min	52.4	42.9
	Within 5 min	38.1	35.7
2. Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes	38.1	50.0
	No	61.9	50.0
3. Which cigarette would you hate most to give up?	The first one in AM	71.4	35.7*
	All others	28.6	64.3*
4. How many cigarettes a day do you smoke?	10 or fewer	9.5	35.7
	11–20	33.3	42.9
	21–30	42.9	14.3
	31+	14.3	7.1
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	47.6	42.9
	No	52.4	57.1
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes	47.6	42.9
	No	52.4	57.1

* $p<.05$.

($M=87.38$, $SE=18.03$), relative to controls ($M=37.14$, $SE=12.76$), demonstrated significantly faster RT following nicotine patch compared to baseline, $F(1,33)=4.21$, $p<.05$ (see Fig. 2). Paired samples t -tests indicated participants with schizophrenia showed significantly faster RT at nicotine patch ($M=690.43$ ms) compared to baseline ($M=777.81$ ms; $t_{20}=4.85$, $p<.001$) or withdrawal conditions ($M=765.81$ ms; $t_{20}=4.91$, $p<.001$). Controls also improved RT at nicotine patch ($M=568.86$ ms) compared with baseline ($M=606.00$ ms, $t_{13}=2.91$, $p=.01$) or withdrawal conditions ($M=613.00$ ms, $t_{13}=2.22$, $p<.05$).

3.3.3. Accuracy

Accuracy rates were submitted to a 2×3 mixed-model ANOVA: group (schizophrenia, control) as the between-subject variable, session (baseline, withdrawal, nicotine) as the within-subject variable. Results indicated trend effects of group, $F(1,33)=3.33$, $p=.077$, and session, $F(2,32)=2.67$, $p=.085$, without significant interaction (see Fig. 3). Participants with schizophrenia demonstrated a tendency toward decreased accuracy (93.3%) in comparison to normal controls (97.9%). Additionally, across groups accuracy rates tended to differ according to nicotine levels, with superior functioning at nicotine patch (97.1%) in comparison to baseline (95.2%) or withdrawal (94.4%).

Exploratory independent-samples t -tests indicated, at baseline, accuracy rates in schizophrenia (92.4%) tended to be more impaired than in controls (98.1%), $t_{23}=1.85$, $p=.077$. Following withdrawal, accuracy rates were significantly worse in schizophrenia participants (91.6%) than controls (97.2%), $t_{26}=2.18$, $p<.05$. Importantly, accuracy rates following nicotine patch *did*

not differ between groups, $t_{26}=1.46$, $p=.16$ (schizophrenia: 95.9% and controls: 98.3%). Additional evidence from paired-samples t -tests in schizophrenia demonstrated a near significant difference between accurate responding at withdrawal (91.6%) and following nicotine patch (95.9%), $t_{20}=2.00$, $p=.059$.

4. Discussion

The study examined the effects of nicotine on ANT performance in schizophrenia. Results indicated that the groups did not differ in performance on either of three ANT measures (alertness, orienting, and executive) across baseline, patch, and withdrawal conditions. However, compared to controls, the participants with schizophrenia showed faster ANT RT for the nicotine patch in relation to the baseline condition. The participants with schizophrenia also showed reduced ANT accuracy at withdrawal but not at patch condition. These results suggest that overall processing speed and accuracy are affected differently by nicotine levels in schizophrenia, with evidence supporting greater impairment from withdrawal and greater improvement from nicotine administration.

The evidence of greater performance improvement with nicotine replenishment in schizophrenia may help to explain increased rates of cigarette use. Given improved neurocognitive functioning with nicotine, persons with schizophrenia may smoke as a means to alleviate cognitive decline due to the effects of illness and/or medication (Glassman, 1993). Even though reaction time was significantly poorer in schizophrenia across and within nicotine conditions, comparisons between conditions demonstrated greater benefit when administered nicotine directly. While controls also benefited from nicotine administration, the impact on reaction time was not nearly as great as it was observed in the schizophrenia group.

Accuracy of responses in schizophrenia also demonstrated an influence of nicotine. It was expected that participants with schizophrenia would show more impaired accuracy across and within nicotine conditions (Gooding et al., 2006; Wang et al., 2005), though similar rates to controls are known in those with paranoid schizophrenia (Neuhaus et al., 2007). In fact, accurate information processing was most impaired following nicotine withdrawal. Most importantly, the accuracy rates at nicotine patch did not differ from control smokers. This finding suggests that a controlled delivery of nicotine, immediately following the withdrawal condition (where participants with schizophrenia were significantly less accurate than normal controls), resulted

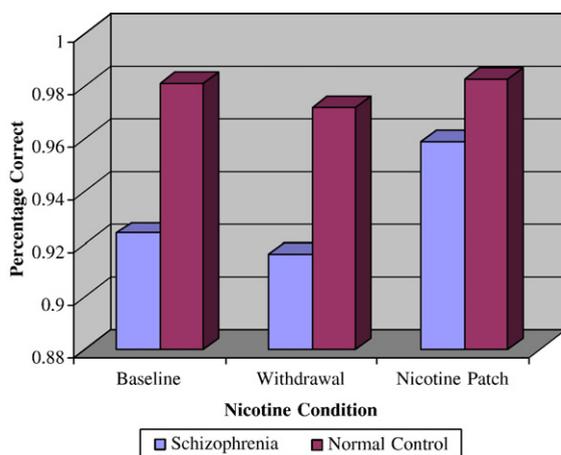


Fig. 3. Accuracy rate differences between subject groups for each nicotine condition.

in significantly improved performance to a level found in the control group. Therefore, in schizophrenia, nicotine depletion has greater adverse effects on accuracy while nicotine administration ameliorates these deficits to levels of a non-psychiatric population.

Nicotine level did affect attention network functioning across groups. Specifically, in both groups, the ability to resolve conflicting information in the executive attention network was improved when assessed at nicotine patch in comparison to existing baseline functioning. This higher order attention network may benefit more by controlled nicotine delivery than other networks. While we did not demonstrate group differences on the attention network task, follow-up research is warranted to explore this effect in schizophrenia given reported executive network dysfunction (Gooding et al., 2006; Wang et al., 2005).

Previous research has identified unique deficits of executive attention functioning in schizophrenia (Gooding et al., 2006). With statistically similar performance between groups on alerting and orienting attention networks, Gooding et al. (2006) point to a specificity of executive attention dysfunction, which is consistent with other (Neuhaus et al., 2007), but not all studies (i.e., orienting network, Wang et al., 2005; alerting network, Nestor et al., 2007). While a lack of significant differences between groups in attention network functioning in this study does not clarify the discrepancies reported in the literature, it does provide additional evidence of the variability of attention functioning in schizophrenia. Given substantial evidence of attention deficits in schizophrenia (Nestor et al., 2001), follow-up examination of the characteristics associated with attention dysfunction in schizophrenia is warranted.

Smokers with schizophrenia demonstrated increased nicotine levels across and within nicotine conditions with significantly higher levels in the patient group at withdrawal. This group difference represents a noteworthy clinical and empirical finding. Increased nicotine levels in schizophrenia may relate to differences in metabolism, behavioral smoking patterns and/or study non-compliance. Increased levels of cotinine, the principal metabolite of nicotine, are reported in schizophrenia (Strand and Nyback, 2005; Jacobsen et al., 2004). Williams et al. (2005) refute the idea that metabolism of nicotine is slower in schizophrenia although they acknowledge that their evaluation examined a subset of enzymes associated with nicotine metabolism. Tidey et al. (2005) identified more intense smoking behavior in schizophrenia including shorter inter-puff intervals and greater total number of puffs/cigarette. In our study, participants did not provide

carbon monoxide samples prior to withdrawal assessment, which may indicate noncompliance with the 8-hour withdrawal period. Nonetheless, salivary nicotine levels did follow the expected pattern in both groups (nicotine patch > baseline > withdrawal), which allowed for comparisons between conditions.

In conclusion, nicotine levels had a greater impact on reaction time and accuracy rates in schizophrenia than in control smokers. Overnight nicotine withdrawal resulted in greater impairment of accuracy in the schizophrenia group while nicotine administration provided greater improvement than that observed in the control group. Nicotine provided greater reaction time benefit in schizophrenia. Despite differences in nicotine levels and a lack of significant group differences in attention network function, these results suggest that cigarette smoking behavior provides ameliorative neurocognitive effects in schizophrenia. Future research on neurocognitive effects of nicotine in schizophrenia will aid in the understanding of increased smoking in this group.

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Contributors

Authors AhnAllen and Nestor designed the study and wrote the protocol. Author AhnAllen managed the literature searches and analyses. Authors AhnAllen and Nestor undertook the statistical analysis, and author AhnAllen wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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