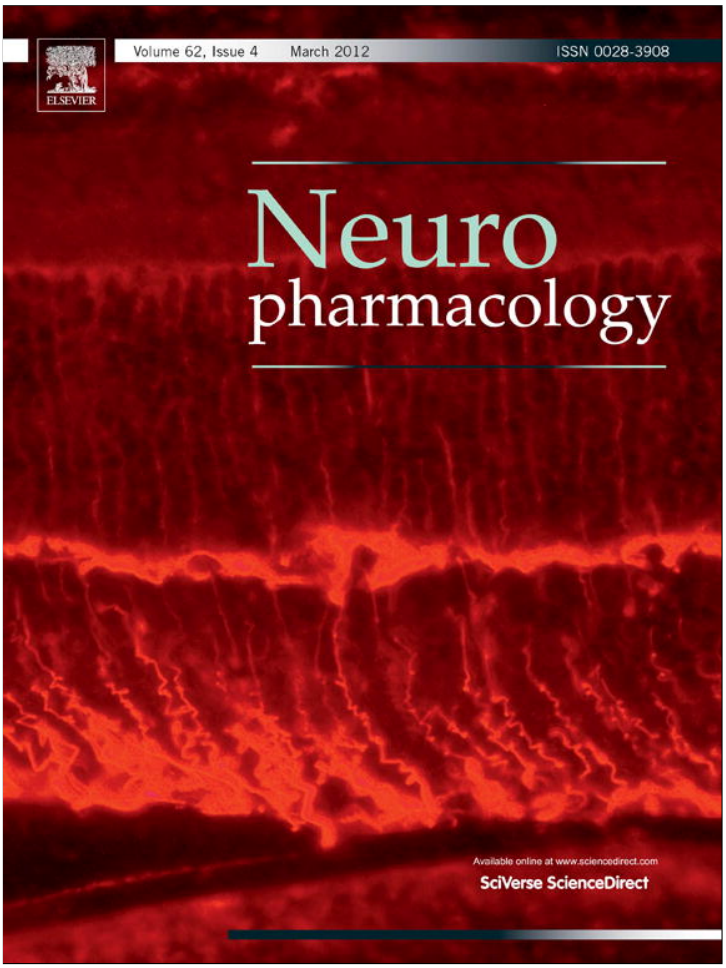

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Effects of smoking history on selective attention in schizophrenia

Constanze Hahn [a,1], Eric Hahn [b,1], Michael Dettling [b], Onur Güntürkün [a], Thi Minh Tam Ta [b], Andres H. Neuhaus [b,*]

[a] Department of Biopsychology, Ruhr University, Bochum, Germany
[b] Department of Psychiatry and Psychotherapy, Charité University Medicine, Campus Benjamin Franklin, Berlin, Germany

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ABSTRACT

Smoking prevalence is highly elevated in schizophrenia compared to the general population and to other psychiatric populations. Evidence suggests that smoking may lead to improvements of schizophrenia-associated attention deficits; however, large-scale studies on this important issue are scarce. We examined whether sustained, selective, and executive attention processes are differentially modulated by long-term nicotine consumption in 104 schizophrenia patients and 104 carefully matched healthy controls. A significant interaction of 'smoking status' × 'diagnostic group' was obtained for the domain of selective attention. Smoking was significantly associated with a detrimental conflict effect in controls, while the opposite effect was revealed for schizophrenia patients. Likewise, a positive correlation between a cumulative measure of nicotine consumption and conflict effect in controls and a negative correlation in patients were found. These results provide evidence for specific directional effects of smoking on conflict processing that critically dissociate with diagnosis. The data supports the self-medication hypothesis of smoking in schizophrenia and suggests selective attention as a specific cognitive domain targeted by nicotine consumption. A potential mechanistic model explaining these findings is discussed.

1. Introduction

Smoking prevalence is elevated in people with schizophrenia compared to the general population and other psychiatric disorders with estimates ranging from 60 to 90%; moreover, schizophrenia patients also exhibit heavier smoking patterns compared to the general population (Winterer, 2010). It has been repeatedly proposed that tobacco smoking may constitute a form of self-medication by schizophrenia patients. Several lines of reasoning support this assumption: First, schizophrenia patients smoking high-nicotine cigarettes compared to denicotinized ones seem to exhibit transiently reduced negative symptoms and perform better in a verbal memory task (Smith et al., 2002). Next, variations in the gene coding for nicotinic alpha7 receptors have been associated with a deficit of P50 auditory sensory gating and schizophrenia (Leonard et al., 2007). Finally, nicotine has also been shown to temporarily improve a number of neurocognitive deficits associated with schizophrenia (Avila et al., 2003; Depatie et al., 2002; Sacco et al., 2005). In sum, this cumulating evidence suggests that at least some cognitive domains are enhanced by nicotine intake in schizophrenia patients.

Against this background, subsequent pharmacological challenge studies have attempted to elucidate and to further characterize cognitive domains thought to be targeted by nicotine consumption in schizophrenia. Apart from effects on episodic memory (Jubelt et al., 2008) and working memory (George et al., 2002), current evidence also hints towards alleviation of attention deficits by nicotine. For instance, Jacobsen and colleagues (Jacobsen et al., 2004) reported that nicotine differentially improved performance of schizophrenia patients during a dichotic two-back task, depending on whether or not they were smokers. In contrast, healthy controls generally performed worse after a nicotine challenge. In a recently published naturalistic study, first-episode schizophrenia patients who smoked exhibited a superior baseline performance compared to non-smoking patients in the selective and sustained attention measures (Segarra et al., 2011). Also nicotine exposure to non-smoking schizophrenia patients (Barr et al., 2008; Harris et al., 2004) and nicotine application after abstinence (Sacco et al., 2005) demonstrate an improvement of attentional deficits by nicotine. As these studies employed mostly

* Corresponding author. Department of Psychiatry and Psychotherapy, Charité University Medicine Berlin, Campus Benjamin Franklin, Eschenallee 3, 14050 Berlin, Germany. Tel.: +49 30 8445 8412; fax: +49 30 8445 8393.
E-mail address: andres.neuhaus@charite.de (A.H. Neuhaus).
[1] These authors contributed equally to this work.

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tests that assess sustained attention (e.g. Digit Symbol Test and versions of the Continuous Performance Test), this specific facet of attention seems particularly suited to further examine the influence of nicotine on cognition in schizophrenia.

In the current study, we investigated the impact of tobacco smoking on behavioral surrogate parameters of sustained, selective, and executive visual attention in a large cohort of schizophrenia patients and carefully matched healthy control participants in a cross-sectional design. By realizing this large-scale study approach, we also aimed to narrow the gap between pharmacological challenge and clinical observation, since challenge studies following smoking abstinence are likely to be confounded by withdrawal phenomena, and findings in non-smoking schizophrenia patients may not generalize to those who smoke (Goff et al., 1992).

2. Materials and methods

2.1. Participants

One hundred-four schizophrenia patients participated in this study. They met DSM-IV criteria for schizophrenia and were clinically stable. Current substance intake other than nicotine consumption was excluded by urinary drug screening. None of the included patients had a history of severe medical disorder, severe neurological disorder, or electroconvulsive therapy. All patients were recruited from the inpatient unit and outpatient clinic (83 % inpatients vs. 17 % outpatients in each group, i.e. smokers and non-smokers) at the Department of Psychiatry, Campus Benjamin Franklin, Charité University Medicine Berlin, Germany. Of note, all inpatients had unrestricted access to cigarettes and a smoker's room. All patients received typical or atypical antipsychotic medication: amisulpride ($N = 20$), aripiprazole ($N = 19$), clozapine ($N = 34$), flupentixol ($N = 7$), olanzapine ($N = 13$), perazine ($N = 3$), quetiapine ($N = 11$), risperidone ($N = 35$), ziprasidone ($N = 5$). Sixty-four patients received an antipsychotic mono-therapy and 40 patients received an antipsychotic combination therapy. Calculation of chlorpromazine equivalents was done following the suggestion of Andreasen et al. (2010). Current intake of benzodiazepines or benztropine as well as presence of extrapyramidal symptoms were exclusion criteria. PANSS ratings were performed by author EH within one week after neuropsychological testing.

One hundred-four healthy control participants were recruited via advertisements in a local newspaper and on the homepage of the Department of Psychiatry, Charité. Controls were carefully matched for age, sex, and variables related to smoking behavior, including smoking status, severity of nicotine dependence, and lifetime nicotine consumption. No control participant had a history of substance abuse other than tobacco smoking, any psychiatric axis I disorder according to DSM-IV, or any other severe medical or neurological disorder, and had never received any psychopharmacological treatment. A first-degree family history of psychiatric illness led likewise to exclusion from the study. All control participants were examined by a certified psychiatrist prior to inclusion in this study.

Participants were classified as non-smokers (<5 cigarettes in lifetime) or smokers (daily smoking for at least 6 months); former/abstinent smokers were not included in this study. Distribution of smoking status and sex was balanced across groups with 22/18 female/male non-smokers and 26/38 female/male smokers within each group to exclude potential effects of sex on cognition. A cross-sectional estimate of severity of nicotine dependence was provided by the Fagerstroem Test for Nicotine Dependence (Heatherton et al., 1991). A longitudinal measure of lifetime nicotine consumption was provided by quantification of cigarette pack years that were calculated as 20 cigarettes per day times the number of years as a smoker (e.g. Lu et al., 2011).

All participants were right-handed, reported normal or corrected-to-normal vision, and were of Caucasian ethnicity. An estimate of (pre-morbid) verbal IQ is given by the German Mehrfach–Wortschatz-Test (multiple choice vocabulary test; Lehrl et al., 1995). Clinical and demographic data of patients and controls stratified by smoking status are summarized in Table 1. All participants gave written informed consent before participating in this study. The study protocol was approved by the ethics committee of the University Hospital Benjamin Franklin, Charité University Medicine, Berlin, Germany, and the study was conducted in accordance with the Declaration of Helsinki and its amendments.

2.2. Cognitive test battery

Prior to the experiment, participants were allowed to smoke ad libitum. Testing was conducted after approximately 1 h of nicotine abstinence, thus minimizing both acute nicotine and nicotine withdrawal effects (Stein et al., 1998). All participants completed a cognitive test battery, including Continuous Performance Test–Identical Pairs (CPT–IP), Attention Network Test (ANT), and Wisconsin Card Sorting Test (WCST) on a 17-inch cathode ray tube monitor. Behavioral responses were collected via response keys on a keyboard.

The CPT–IP was developed as a test of sustained visual attention in schizophrenia patients and healthy controls (Cornblatt et al., 1988). Using their dominant hand, participants pressed a mouse key as quickly as possible when two identical pairs of numbers were presented in sequence. Following 10 practice trials with three-digit numbers, a total of 150 trials with four-digit numbers were presented with an invariant presentation rate of one stimulus per 1000 ms and a stimulus duration of 50 ms. Thirty out of 150 stimuli served as target stimuli. Outcome measures were d', a standard measure in signal detection theory representing the signal-to-noise ratio, hit rate (correct hits), and mean reaction time (RT) for correct hits.

The ANT is a test of selective attention that combines a cued detection paradigm with a flanker task (Fan et al., 2002). Attention network effects of alerting, orienting, and conflict were calculated as the difference in RT between task conditions. Alerting refers to the behaviorally beneficial effect of increased response preparation following a temporal cue, and is computed as RT targets (no previous cue) minus RT targets (previous double cue). Orienting refers to the behaviorally beneficial effect of increased response preparation following spatial cueing, and is computed as RT targets (previous center cue) minus RT targets (previous spatial cue). Conflict refers to the behaviorally detrimental effect of a flanker compatibility conflict, and is computed as RT incompatible targets minus RT compatible targets.

The WCST measures executive attention by assessing estimates of establishing and shifting cognitive sets (Heaton, 1981). Participants are instructed to sort stimulus cards on the basis of color, form, or number of symbols. The only feedback provided is whether the current response was correct or incorrect. The sorting rule changes after 10 consecutive correct responses. The test is discontinued when the participant has learned two iterations of each sorting rule, or completed 128 trials. The primary outcome measures used for this study were failures to maintain set (cognitive set maintenance), number of perseverative errors (cognitive set shifting), and numbers of categories completed.

Table 1
Summary of demographic and clinical data.

	Patients			Controls		
	Smokers	Non-smokers	Total	Smokers	Non-smokers	Total
N (female/male)	64 (26/38)	40 (22/18)	104 (48/56)	64 (26/38)	40 (22/18)	104 (48/56)
Age [years]	33.63 ± 10.9	37.58 ± 10.4	35.14 ± 10.8	32.36 ± 6.9	34.78 ± 12.4	33.29 ± 9.4
Pre-morbid verbal IQ	103.68 ± 11.8	108.67 ± 14.9	105.59 ± 13.3[b]	111.68 ± 13.5	117.20 ± 15.0	113.83 ± 14.3
Nicotine consumption [pack years]	11.29 ± 9.3	–	–	10.75 ± 8.2	–	–
Cigarettes per day	21.48 ± 11.4	–	–	17.78 ± 10.4	–	–
Years of smoking	14.70 ± 6.8	–	–	12.91 ± 7.7	–	–
FTND score	5.18 ± 2.4[a]	–	–	3.83 ± 2.1	–	–
DOI [years]	6.73 ± 7.4	9.17 ± 9.2	7.65 ± 8.2	–	–	–
N episodes	3.40 ± 3.0	3.69 ± 2.9	3.51 ± 2.9	–	–	–
PANSS positive scale	14.29 ± 5.3	12.73 ± 4.9	13.31 ± 5.1	–	–	–
PANSS negative scale	18.34 ± 6.2	16.46 ± 6.7	17.16 ± 6.5	–	–	–
PANSS general scale	33.97 ± 10.7	30.25 ± 9.7	31.66 ± 10.2	–	–	–
CPZ equivalents [mg]	525.95 ± 354.2	484.64 ± 318.4	500.53 ± 331.6	–	–	–

FTND, Fagerstroem Test for Nicotine Dependence; DOI, duration of illness; PANSS, Positive And Negative Syndrome Scale; CPZ, chlorpromazine.
[a] significantly higher than in control smokers ($T_{47} = 2.066$; $p < .05$).
[b] significantly lower than in controls ($T_{203} = 4.282$; $p < .01$).

2.3. Statistical analyses

Statistical calculations were conducted using PASW 18.0 (Predictive Analytics Software; SPSS Inc., Chicago, IL, US). Demographic data were analyzed with χ^2 test and *t*-tests for independent samples. The following dependent variables were chosen: d', hit rate, hit reaction time (CPT–IP); alerting, orienting, conflict (ANT); failure to maintain set, categories completed, perseverative errors (WCST). Each dependent variable was subjected to a 2 × 2 × 2 ANCOVA, with diagnostic group, sex, and smoking status as between-subject factors and with Fagerstroem score and pre-morbid verbal IQ as co-variates. Correlation analyses were performed as Pearson correlations. To control for multiple comparisons, tests for differences of cognitive performance, including confirmatory post hoc tests and correlation analyses, were performed as two-tailed tests with a Bonferroni-corrected alpha level set at $p < .05$. Given the opposite directionality of hypotheses, tests of demographic (within and between diagnostic groups) and clinical variables (within diagnostic group) were performed as uncorrected two-tailed tests with an alpha level set at $p < .05$.

3. Results

Table 2 summarizes neuropsychological data together with main effect of diagnostic group and interaction effects of diagnostic group × smoking status.

3.1. Sustained attention (CPT–IP)

Although significant main effects of diagnostic group were found with controls outperforming the patient group in terms of signal-to-noise-ratio ($F_{1,117} = 17.576$; $p < .001$) as well as hit rate ($F_{1,117} = 42.059$; $p < .001$), the CPT–IP did not reveal any interaction effects of diagnostic group × smoking status. Also, no significant main effects of smoking status, sex, Fagerstroem score, or verbal intelligence were found.

3.2. Selective attention (ANT)

In the absence of main effects of diagnostic group or smoking status, a significant interaction of diagnostic group × smoking status was obtained for the conflict condition of the ANT ($F_{1,117} = 13.483$; $p < .01$). Post hoc *t*-tests revealed that in the control group, smoking was associated with a higher conflict effect compared to non-smoking individuals (smokers: 101.54 ms ± 36.7 ms vs. non-smokers: 84.84 ms ± 23.1 ms; $p < .05$); a complementary pattern was revealed for schizophrenia patients (smokers: 83.42 ms ± 36.4 ms vs. non-smokers: 105.33 ms ± 54.2 ms; $p < .05$). Both linear regression (Fig. 1) and Pearson correlation indicated a positive association between conflict effect and several measures of nicotine consumption in controls (cigarette pack years: $r = .214$; $p < .05$; years of smoking: $r = .332$; $p < .001$; Fagerstroem score: $r = .234$; $p = .051$), and a negative association in schizophrenia patients (cigarette pack years: $r = -.195$; $p < .05$; years of smoking: $r = -.235$; $p < .05$; Fagerstroem score: $r = -.236$; $p = .072$). No correlation was obtained between conflict effect and any of the clinical variables in schizophrenia patients.

Interestingly, a significant effect of sex was observed for the same cognitive parameter, i.e. conflict ($F_{1,117} = 6.702$; $p < .05$). Post hoc testing indicated that male participants had lower conflict scores than female participants across groups (86.63 ms ± 36.3 ms vs. 101.48 ms ± 41.7 ms; $p < .01$). When stratified for diagnostic groups, this effect was found to be primarily driven by the patient group (males: 80.92 ms ± 40.1 ms vs. females: 104.59 ms ± 47.4 ms; $p < .05$), with insignificant differences between sexes in controls (males: 92.34 ms ± 31.4 ms vs. females: 98.36 ms ± 34.8 ms). However, there was no significant tripartite interaction of diagnostic group × smoking status × sex. Moreover, no significant main effects of Fagerstroem score or verbal intelligence were detected.

3.3. Executive attention (WCST)

Significant main effects of diagnostic group were found for perseverative errors ($F_{1,117} = 5.059$; $p < .001$) and number of categories completed ($F_{1,117} = 4.419$; $p < .001$) with controls committing fewer errors and completing more categories. However, no significant interaction of 'diagnostic group' × 'smoking status' was observed. No significant main effects of smoking status, sex, Fagerstroem score, or verbal intelligence were found.

4. Discussion

The current study addresses accumulating evidence that chronic nicotine consumption may be a critical factor in modulating several attentional domains in schizophrenia and, to our knowledge, contributes the largest cross-sectional study on behavioral effects of smoking history in schizophrenia. Our results reveal a specific effect of chronic nicotine exposure on conflict processing efficiency as a surrogate parameter of selective attention. Importantly, this smoking-related effect dissociates with diagnosis, in that efficiency of conflict processing declines with smoking history in healthy controls, whereas it improves in schizophrenia patients with the duration of chronic smoking. This dissociation adds to the findings of previous studies, reporting beneficial effects of chronic smoking on attention and working memory in schizophrenia (Barr et al., 2008; George et al., 2002; Harris et al., 2004; Jacobsen et al., 2004; Segarra et al., 2011) and detrimental effects on cognitive performance measures in healthy controls (Ernst et al., 2001; Lawrence et al., 2002). As a minor finding, a sex difference between male and female schizophrenia patients regarding efficiency of conflict processing was detected. However, this particular result was not further pursued, as it essentially replicates a previous study on sex differences in selective attention in schizophrenia (Urbanek et al., 2009) and does not contribute to the understanding of the core finding of this study, i.e. an interactive effect of smoking behavior and diagnosis on selective attention.

Our main result can be explained by a single coherent mechanism that is based on well established findings of (I) a prefrontal

Table 2
Summary of neuropsychological data.

		Patients		Controls		*F* Group	*F* group × Smoking status
		Smokers	Non-smokers	Smokers	Non-smokers		
CPT–IP:	d'	0.98 ± 0.7	0.91 ± 0.8	1.56 ± 0.8	1.60 ± 0.8	17.576**	.014
	Hit rate	0.47 ± 0.3	0.47 ± 0.3	0.72 ± 0.2	0.78 ± 0.2	42.059**	.098
	Hit reaction time [ms]	553.65 ± 129.2	480.14 ± 195.8	545.51 ± 69.9	526.52 ± 45.7	.481	1.023
ANT:	Alerting [ms]	40.64 ± 31.4	46.90 ± 37.8	42.14 ± 27.4	40.80 ± 21.1	.765	.079
	Orienting [ms]	53.56 ± 33.3	64.90 ± 36.7	48.58 ± 22.3	54.90 ± 23.4	.469	.452
	Conflict [ms]	83.42 ± 36.4	105.33 ± 54.2	101.54 ± 36.7	84.84 ± 23.1	2.118	13.483**
WCST:	Failure to maintain set	1.08 ± 1.3	1.03 ± 1.3	1.02 ± 1.1	0.83 ± 1.1	.043	.800
	Perseverative errors	17.02 ± 14.1	13.23 ± 8.2	9.63 ± 5.8	10.58 ± 7.0	5.059*	1.340
	Categories completed	4.69 ± 1.9	5.23 ± 1.5	5.81 ± 0.6	5.60 ± 1.2	4.419*	1.509

*$p < .05$; **$p < .001$; CPT–IP, Continuous Performance Test–Identical Pairs; ANT, Attention Network Test; WCST, Wisconsin Card Sorting Test.

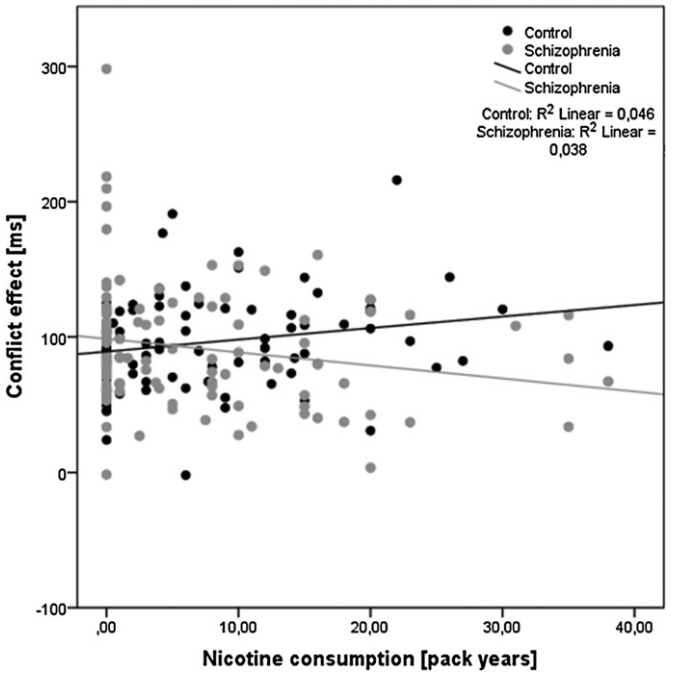

Fig. 1. Combined scatter plot of lifetime nicotine consumption in pack years (abscissa) vs. behavioral conflict effect assessed with Attention Network Test (ordinate) for healthy controls and schizophrenia patients.

dopaminergic deficit in schizophrenia (Goldman-Rakic et al., 2001) and (II) a persistent enhancement of dopamine release from ventral tegmental area dopaminergic neurons by nicotine (Imperato et al., 1986). The prefrontal top–down regulation of attention is modulated by the dopaminergic system that acts at D1 receptors to narrow neuronal tuning, to decrease network noise and to thus enhance synaptic strength that then mediates the stabilization of prefrontal representations (Arnsten, 2011; Durstewitz et al., 1999; Rose et al., 2010). As a consequence, and corresponding to the nicotine self-medication hypothesis of schizophrenia, nicotine consumption may in fact compensate deficient prefrontal dopamine-mediated cognition in schizophrenia via D1 receptors. The dopaminergic effect on D1 follows a non-linear, inverted U-function (Vijayraghavan et al., 2007) where schizophrenia patients and healthy controls are located on different positions. Corresponding with the prefrontal D1 deficit, it is conceivable that schizophrenia patients are located on the ascending left side of the inverted U curve, while healthy controls are located around the top of the curve, indicating optimal D1 receptor activation. Thus, a nicotine-mediated right shift on this curve differentially affects attentional functions of both groups. Consequently, and as previously outlined by George et al. (2002), nicotine increases attentional performance in schizophrenia patients, but decreases performance in healthy controls, which has also been observed in other studies (Ernst et al., 2001; Jacobsen et al., 2004; Lawrence et al., 2002).

Hypothetically, anterior cingulate cortex (ACC) constitutes the neuroanatomical substrate of the observed dissociation. The key property of selective attention is to focus on instruction-driven attentional processes at the same time as having to disregard distracters. Selective attention is therefore assessed with paradigms generally involving conflicting stimuli or stimuli inducing prepotent responses that have to be inhibited. These properties are part of many cognitive paradigms, such as flanker tasks, Stroop tasks, and go-nogo tasks, all of which are associated with ACC function (e.g. Barch et al., 2001; Carter et al., 1998; Fan et al., 2005; Paus et al., 1993; Van Veen et al., 2001). ACC function has been linked to dopamine D1 receptors by recent multireceptor autoradiography studies (Palomero-Gallagher et al., 2009), by event-related potential studies that identified ACC as the source of the D1-mediated error-related negativity (Gehring and Knight, 2000), and by genetic dissection studies on ACC function (Krämer et al., 2007).

In schizophrenia, ACC activity is typically decreased in selective attention tasks (Ford et al., 2004; Kerns et al., 2005), consistent with a prefrontal hypodopaminergic state (Goldman-Rakic et al., 2001). Following nicotinic stimulation, ACC activity in schizophrenia typically increases (Hong et al., 2011; Jacobsen et al., 2004; Minzenberg et al., 2009; Tregellas et al., 2005). Of particular interest, and consistent with our findings, Tanabe and colleagues (Tanabe et al., 2006) investigated the effect of a nicotine gum on smooth pursuit eye movements in 16 schizophrenia patients and 16 matched controls. They found a dissociation of ACC activity following nicotinic stimulation, with decreased ACC activity in healthy controls, but increased activity in schizophrenia. A similar activation pattern, a higher increase of ACC activity in schizophrenia patients compared to healthy controls, has been described during a combined selective attention/working memory task by Jacobsen et al. (2004).

Apart from the positive finding in selective attention, no impact of smoking history was found for sustained and executive attention. For both attention domains, however, mixed findings have been obtained regarding the impact of smoking status in schizophrenia. Different versions of the CPT have been implemented to assess sustained attention and highly variable patterns of results were reported. Impact of smoking or nicotine challenge has been described for the variables 'hit rate' (Sacco et al., 2005), 'mean RT' (Barr et al., 2008; Segarra et al., 2011), and 'errors' (Segarra et al., 2011). Of note and consistent with our study, the most commonly reported measure d' does not seem to be affected by smoking status. In the case of executive attention, as measured with the WCST, both negative (Sacco et al., 2005) and positive findings (Rabin et al., 2009) were reported. In sum, the existing literature on the impact of smoking status is heterogeneous, possibly owing to the usually low number of subjects included. The incremental value of the present study is a high number of schizophrenia and control participants, thereby decisively reducing the risk of spurious findings.

This study had some limitations that have to be acknowledged. First, no objective control of nicotine dose is available for this study. Although we sought to minimize both acute nicotine and nicotine withdrawal effects by testing after approximately 1 h of nicotine abstinence, it cannot be ruled out that the resulting data is heterogeneous due to individual smoking habits. A control via measurement of serum cotinine levels would have been a more favorable measure of nicotine dose than the history of smoking behavior. Next, the cross-sectional nature of our study does not permit to conclude whether the observed associations between chronic smoking patterns and selective attention in schizophrenia were caused by smoking or whether they preceded its initiation. Further, schizophrenia patients displayed lower pre-morbid verbal intelligence and heavier nicotine consumption than healthy controls. These confounds, however, have been controlled for statistically, and, importantly, do not explain the directionality of the results observed in the present study.

In conclusion, the current study demonstrates a divergent cognitive effect of smoking in healthy controls and schizophrenia patients and further substantiates the hypothesis that smoking is used as self-medication of a selective attention deficit associated with schizophrenia. Specifically, and in accordance with previous neurobiological findings, our data provide evidence that chronic nicotine intake reduces distractibility in schizophrenia patients, as evidenced by improved target detection in the presence of competing information, which is a fundamental property of

selective attention. A single coherent mechanism is offered as a model to explain the effects of nicotine-dopamine interactions that lead to the observed behavioral dissociation. As a consequence, smoking is disadvantageous for healthy participants with a priori favorable dopamine levels, but reinstates an advantageous D1 state in schizophrenia patients who otherwise suffer from a marked prefrontal dopamine deficit.

Conflict of interest

None.

Disclosure

All authors declare that they do not have any biomedical financial interest or potential conflicts of interest related to this study or its publication.

None of the authors received compensation for professional services within the last three years or anticipates compensation in the near future.

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