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ORIGINAL PAPER

Effects of nicotine on social cognition, social competence and self-reported stress in schizophrenia patients and healthy controls

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Abstract More than 80 % of patients diagnosed with schizophrenia are nicotine-dependent. Self-medication of cognitive deficits and an increased vulnerability to stress are discussed as promoting factors for the development of nicotine dependence. However, the effects of nicotine on social cognition and subjective stress responses in schizophrenia are largely unexplored. A 2 × 2-factorial design (drug × group) was used to investigate the effects of nicotine versus placebo in smoking schizophrenia patients and healthy controls after 24 h of abstinence from smoking. Participants performed a facial affect recognition task and a semi-standardized role-play task, after which social competence and self-reported stress during social interaction were assessed. Data analysis revealed no significant group differences in the facial affect recognition task. During social interaction, healthy controls showed more non-verbal expressions and a lower subjective stress level than schizophrenia patients. There were no significant effects of nicotine in terms of an enhanced recognition of facial affect, more expressive behaviour or reduced subjective stress during social interaction. While schizophrenia patients unexpectedly recognized facial affect not significantly worse than healthy controls, the observed group differences in subjective stress and non-verbal expression during social interaction in the role-play situation are in line with previous findings. Contrary to expectations derived from the self-medication hypothesis, nicotine showed no significant effects on the dependent variables, perhaps because of the dosage used and the delay between the administration of nicotine and the performance of the role-play.

Keywords Schizophrenia · Nicotine · Social cognition · Social stress · Social skills

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Introduction

Schizophrenia is often associated with comorbid drug and alcohol abuse [1]. In particular, more than 80 % of individuals with chronic schizophrenia are nicotine-dependent [2]. Thus, the rate of smoking in patients with schizophrenia is about two- to fourfold that seen in the general population or in those with other severe mental disorders [3]. Nicotine is already used extensively before the onset of schizophrenia [4], indicating a significant temporal association between the initiation of smoking and the prodromal phase of schizophrenia [5]. The self-medication hypothesis has been discussed in the past decade as a possible explanation for the high rate of smoking, that is,

patients smoke to cope with stress and cognitive impairments [6–9]. Although there is little direct evidence for positive effects of nicotine on stress in schizophrenia patients, several other findings support this hypothesis. Many smoking healthy individuals report that the reduction in stress-associated feelings of discomfort and the feeling of relaxation play a central role in sustaining or resuming their smoking habit [10–12]. Notably, adolescents who had felt relaxed in response to their first exposure to nicotine were more likely to develop nicotine dependence and to report that stress caused craving or a need to smoke [13]. Moreover, stressful life events are one of the main risk factors for relapse in abstinent smokers [14], and craving for nicotine increases after psychosocial stress [15]. Compared with healthy persons, individuals with psychotic disorders more often report stress reduction [16] or a desire for calmness [17] as a main reason for smoking, and they display an increased sensitivity to stressors [18], especially to psychosocial stressors often arising from social interaction [19].

In contrast to the dearth of direct evidence for the effects of nicotine on stress, there is consistent evidence that nicotine has beneficial effects on basic cognitive processes like attention and memory in both healthy individuals [20, 21] and schizophrenia patients [22–24]. However, little is known about nicotine effects on social cognitive processes, that is, those cognitive processes underlying social interaction (e.g. situational understanding, affect recognition and theory of mind) [25]. Social cognitive processes might be more relevant than basic cognitive processes with regard to nicotine effects and the self-medication hypothesis because impairments in social cognition are more closely related to poor social interaction both conceptually and empirically [26, 27] and may contribute to the psychosocial stress of schizophrenia patients during social interaction. In particular, impairments in facial affect recognition as the basic building block of social cognition [28] are one of the most often replicated findings in schizophrenia [29], and there is abundant evidence for a significant relationship between poor facial affect recognition and impairments in social skills [30] and social functioning [27, 31]. In addition to poor social cognition, schizophrenia patients also show restricted expressive behaviour (e.g. restricted facial expression, gestures, prosody) during social interaction [32–36] throughout the course of the disorder, which is often taken as an indicator of poor social skills. Schizophrenia patients' poor recognition of the facial expressions of communication partners, together with their own restricted expressive behaviour, severely hampers interpersonal communication. Subjectively, this probably causes uncertainty and a feeling of strangeness during communication [27], which may constitute a stress component that (further) destabilizes the patient and causes or increases social withdrawal.

Although there is no direct evidence as to how nicotine affects social cognition and social behaviour in schizophrenia patients, different studies have suggested that the processing of facial expressions may be altered by cholinergic enhancement. Administration of the cholinesterase inhibitor physostigmine was shown to activate brain regions relevant to the processing of task-relevant emotional stimuli (fearful faces) and results in an improved processing of these stimuli [37]; for review, see [38]. Functional magnetic resonance imaging (fMRI) studies have shown that nicotine administration induces a dose-dependent increase in neuronal activity in a distributed system of brain regions, including the nucleus accumbens, amygdala, cingulate and prefrontal cortex [39, 40]. Activation in these structures is consistent with nicotine's behaviour-arousing and behaviour-reinforcing properties in humans and may also serve as the basis for nicotine's effects on social interaction. Studies using animal models have shown that nicotine improves and facilitates social interaction [41, 42] and social recognition [43].

Thus, in accordance with assumptions from the self-medication hypothesis of nicotine dependence, it seems conceivable that nicotine ameliorates social cognitive impairments and increased stress sensitivity in schizophrenia patients. Since the effects of nicotine on social cognition and social behaviour as well as on subjective stress during social interactions are largely unexplored, the objective of the present study was to compare the impact of nicotine on facial affect recognition, social competence (assessed by non-verbal behaviour) and stress responses (assessed by subjective feelings of sulkiness, anxiety, etc.) during social interaction in persons with schizophrenia and healthy controls. In general, performance was expected to be poorer and stress responses more intense in the schizophrenia patients. The administration of nicotine was expected to (1) facilitate facial affect recognition and (2) social competence and (3) reduce self-reported stress during social interactions. (4) These effects were expected to be more pronounced in schizophrenia patients than in healthy individuals.

Methods

Design

After 24 h of abstinence from smoking, either nicotine (1 mg) or placebo was administered to smoking schizophrenia patients and smoking healthy controls in a 2 × 2 randomised, double-blind study design with the quasi-experimental between-subjects factor 'group' and the experimental between-subjects factor 'drug'.

Participants

The sample comprised 27 clinically stable outpatients who fulfilled the diagnostic criteria for schizophrenia, assessed

with the Structured Clinical Interview for DSM-IV (SCID; [44]) and 45 healthy controls with no history of a psychiatric disorder. The whole sample was investigated in the context of a comprehensive pharmacological study consisting of fMRI and EEG recordings and different cognitive tasks (see e.g. [45]). The clinical sample was recruited at the Department of Psychiatry and Psychotherapy of the University of Düsseldorf, Germany, and the healthy controls from a population-based database (a database also used for the German Multicenter Study on Smoking-Related Behavior [46]). All participants were smokers scoring ≥4 in the Fagerström Test for Nicotine Dependence (FTND) [47].

Inclusion and exclusion criteria (i.e. negative drug screening and no cardiovascular or organic brain diseases or magnetic implants) were assessed in all participants. Two patients and six controls had to be excluded from the study because they did not fulfil inclusion criteria. Additionally, four patients and seven controls had to be excluded from the data analysis because of physical or psychological discomfort either during the fMRI scan or as a result of smoking deprivation. Thus, the remaining sample consisted of 21 schizophrenia patients (5 female, 16 male; mean age: 34.5 years; mean FTND score: 5.86, range 4–9) and 32 controls (21 female, 11 male; mean age: 32.2 years; mean FTND score: 5.13, range 4–8). The intelligence quotient (IQ) was estimated with the multiple choice vocabulary test (MWT-B, [48]); the patients' IQ (mean IQ = 108) did not differ significantly from that of the healthy controls (mean IQ = 105).

Twelve patients and 16 controls received nicotine, whereas nine patients and 16 controls received placebo.

Assessment

Social cognitive performance: facial affect and age recognition

For the assessment of facial affect recognition, we used 24 cross-culturally validated pictures from the Pictures of Facial Affect (PFA) set by Ekman & Friesen [49] and our own set of validated pictures with affective facial expressions; each picture shows either a female or a male actor expressing one of the basic emotions sadness, fear, anger and disgust.

To control for non-specific effects, 24 pictures of the same actors with neutral facial expressions were used in a control task and the participants were asked to choose the correct age decade for the person (21–30, 31–40, 41–50 or 51–60 years).

The pictures were displayed on a PC monitor in a fixed, pseudo-randomized order for predefined periods. A fixation cross was shown for 1 s before each of the 48 stimuli, which were presented for 4 s each in blocks of four stimuli (4 emotion, 4 age, 4 emotion, etc.). Each block was preceded by short instructions (2 s) and followed by a 20-s pause. Participants had to select the appropriate emotion or age category, respectively, by pressing one of four buttons on Lumitouch key pads® (Photon Control Inc., Burnaby, BC, Canada). The number of correct answers in the facial affect recognition task (across all emotions) and the age recognition task were used as the social cognitive performance measures.

Social competence

To assess the impact of nicotine on non-verbal behaviour and self-reported stress during social interaction, all participants had to complete a semi-standardized conversation skills role-play test of 5 min in length. This behavioural probe is an adaptation of the Maryland Assessment of Social Competence (MASC) battery [50, 51]. In order to challenge social competence (i.e. the ability to adapt adequately to new social situations and to act successfully within such a situation), the role-play task required the participants to meet an unknown person (in all cases, a young female research assistant) and to initiate a conversation with her. The social interaction was videotaped and later examined by two independent, trained raters, who were blind with regard to group and drug. Social competence was rated on a slightly modified version of the Rating Scale for Social Competence (RSSC, [52]), which contains the items 'Facial expression', 'Gestures' as well as 'Global social competence' in addition to the original items. Each item was rated on a scale ranging from 1 to 5 (1 = very bad, in the case of the item 'Nervousness' = very strong; 5 = very good, in the case of the item 'Nervousness' = none). Agreement between the ratings was assessed according to the guidelines of Landis and Koch [53] and found to be between 'almost perfect' and 'fair'.

Self-reported acute mental state

The multidimensional self-report inventory BSKE-30 [54] was used to assess self-reported stress responses. The questionnaire comprises 30 items representing 17 subtests (e.g. relaxation, physical well-being/indisposition, intro-/extraversion and good mood/sulkiness). Items were rated on scales ranging from 0 to 6 (0 = not at all and 6 = very strong).

Procedure

At a baseline visit, written informed consent was obtained, the participants' medical and psychopathological status was assessed and inclusion and exclusion criteria were checked. The experimental investigation took place 3 days

Table 1 Levels of exhaled carbon monoxide (average CO in parts per million ± SD) and Cotinine (average cotinine in ng/mL) before and after overnight nicotine withdrawal

	Day 1		Day 2	
	CO	Cotinine	CO	Cotinine
Smoking patients	25.81 (±16.262)	258.95 (±136.652)	4.10 (±3.793)	68.47 (±57.179)
Smoking healthy participants	17.03 (±9.461)	151.48 (±109.082)	3.31 (±3.345)	30.71 (±35.271)

later, after overnight nicotine withdrawal. Levels of exhaled carbon monoxide (CO) in parts per million (ppm), measured with a Micro 4 Smokerlyzer® (Bedfont Scientific Ltd.), and plasma cotinine immunoassay levels (DRI® Cotinine Assay, Microgenics, Passau, Germany) served as objective measures of compliance with nicotine withdrawal. Values declined from day 1 to day 2 in all participants, indicating their compliance (see mean values in Table 1). The study was approved by the ethics committee of the University of Düsseldorf and conducted in compliance with the Declaration of Helsinki.

Before the experimental session, participants were administered 1 mg (0.5 mg in each nostril) of Nicorette® nasal nicotine spray (McNeil Products Co., or equivalent), which is comparable to smoking one cigarette, or a nasal spray of pepper solution as a placebo. The use of pepper, which has a strong taste and odour, made it difficult for the participants to distinguish between the two conditions.

After the administration of nicotine or placebo, the participants completed the facial affect recognition and control tasks mentioned above and underwent concomitant fMRI and EEG recordings. Two additional tasks (Oddball and Posner Paradigm), also with concomitant fMRI and EEG recordings, were used to assess the effects of nicotine on attentional processes and brain networks. The results of these assessments will be reported elsewhere.

Thereafter, participants performed the social competence role-play test and completed the questionnaire on their self-reported stress level during social interaction. Because of the time needed to perform the preceding tasks and neuroimaging assessments, the average interval between drug administration and the role-play was about 84 min.

Statistical analyses

Data were analysed with PASW Statistics 18. Univariate analyses of variance (ANOVAs) were used to compare cognitive performance in the facial affect and age recognition tasks, the eight components of social competence and the 17 areas of acute mental state in schizophrenia patients and healthy controls under nicotine and placebo. Results were interpreted according to Abt's 'Descriptive Data Analysis' [55], that is, α-adjustments were not applied and results were only interpreted if they occurred in 'near regular' patterns of relevant effect differences.

Results

Social cognitive performance

The two ANOVAs of the participants' cognitive performance in the facial affect and age recognition tasks did not reveal any significant group or drug effects or any interactions (cf. Table 2). The rate of correct answers in the facial affect recognition task was about 69 % (grand mean = 69.2, SD = 19.26), and in the age recognition task about 56 % (grand mean = 55.64, SD = 15.02), mostly irrespective of group and drug condition.

Social competence (RSSC)

The ANOVAs of the participants' non-verbal behaviour during social interaction, assessed by the eight RSSC items, found significant group differences between patients and controls but no drug effects or group-by-drug interactions (cf. Table 2; Fig. 1). Healthy participants were rated as being significantly more socially competent in all areas of non-verbal behaviour except prosody, which only showed a trend towards a group difference.

Self-reported acute mental state (BSKE-30)

The ANOVAs of the participants' self-reported mental state during social interaction revealed significant group differences between schizophrenia patients and controls in six of the 17 items: schizophrenia patients described themselves as less alert, self-confident, extraverted and vital and more introverted and depressed than controls. Additionally, patients tended towards higher ratings on the anxiety and anhedonic reactivity scales than the healthy control sample (cf. Table 2; Fig. 2). Differences between nicotine and placebo were found in only two items: participants felt more extraverted and anxious under nicotine than under placebo (cf. Table 2; Fig. 3).

Correlations between the dependent variables

While performance in the facial affect recognition task and non-verbal behaviour in the role-play task only correlated with respect to the recognition of disgust and the 'facial

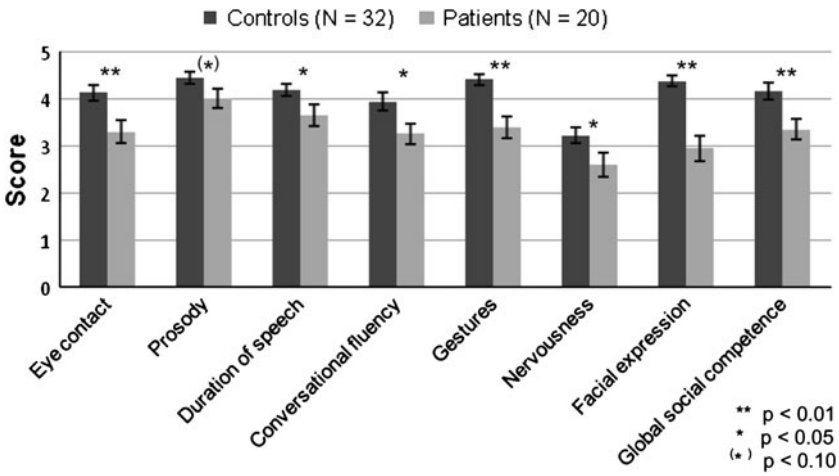

Fig. 1 Social competence ratings in healthy controls and schizophrenia patients (mean ± SEM)

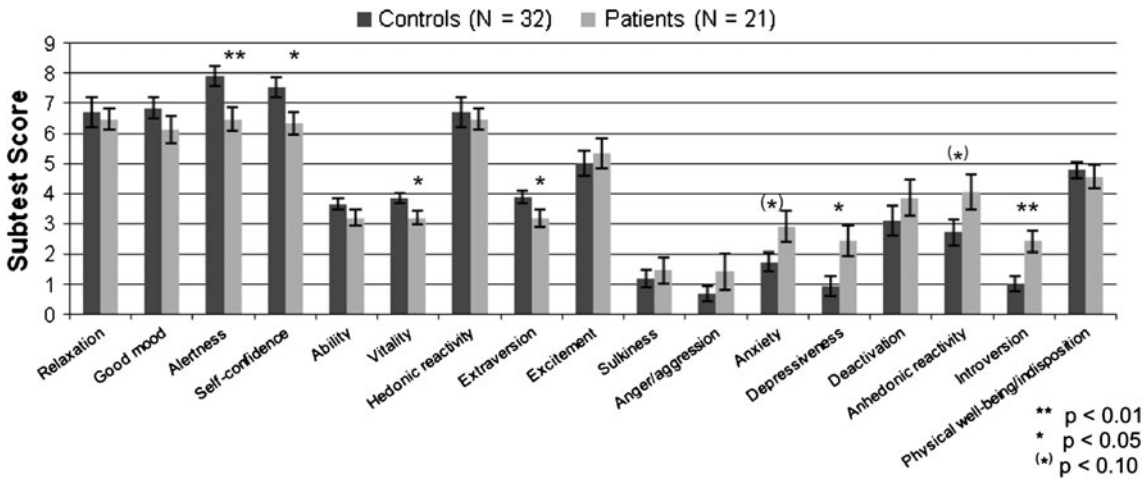

Fig. 2 Self-reported acute mental state in healthy controls and schizophrenia patients (mean ± SEM)

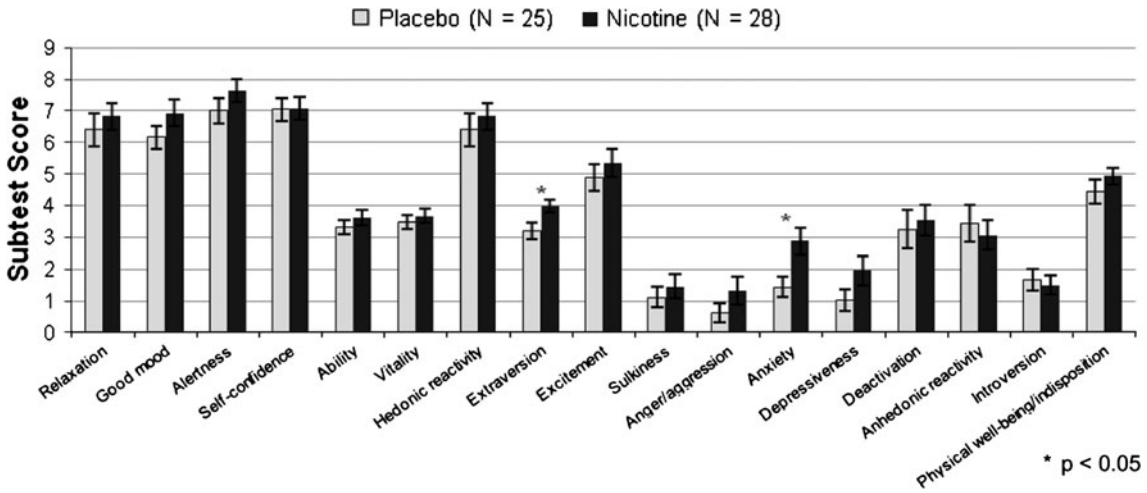

Fig. 3 Self-reported acute mental state under placebo and nicotine (mean ± SEM)

expression' displayed during the role-play ($r = 0.37$, $p < 0.01$), all but one of the scales assessing non-verbal behaviour ('Prosody') were found to significantly correlate with the subjective mental state. Just to name some examples, the BSKE-30 scales 'Alertness' and 'Extraversion' were found to correlate positively ($r = 0.29$ to 0.49,

Table 2 Results of univariate 2 × 2 ANOVAs (group × drug) for measures of social cognition, social competence and self-reported acute mental state during social interaction (effects with $p < 0.05$ are in bold)

	Main effect				Interaction	
	Group		Drug			
	F	*p*	*F*	*p*	*F*	*p*
Social cognitive performance						
Affect recognition	1.96	0.168	0.86	0.359	0.794	0.377
Age recognition	0.005	0.944	0.634	0.430	1.99	0.165
Social competence						
Eye contact	**9.188**	**0.004**	1.688	0.200	0.187	0.667
Prosody	3.158	0.082	0.197	0.659	0.197	0.659
Duration of speech	**5.189**	**0.027**	0.256	0.615	0.256	0.615
Conversational fluency	**6.322**	**0.015**	2.151	0.149	0.395	0.533
Gestures	**19.301**	**0.000**	2.229	0.142	1.530	0.222
Nervousness	**5.477**	**0.023**	1.495	0.227	2.051	0.159
Facial expression	**31.953**	**0.000**	0.966	0.330	0.242	0.625
Global social competence	**8.951**	**0.004**	0.995	0.324	0.111	0.741
Self-reported acute mental state						
Relaxation	0.113	0.738	0.236	0.629	0.472	0.495
Good mood	1.560	0.218	1.560	0.218	0.664	0.419
Alertness	**7.999**	**0.007**	1.787	0.187	0.228	0.636
Self-confidence	**5.491**	**0.023**	0.034	0.855	0.034	0.855
Ability	2.128	0.151	0.926	0.341	0.001	0.975
Vitality	**5.151**	**0.028**	0.762	0.387	0.060	0.808
Hedonic reactivity	0.113	0.738	0.236	0.629	0.472	0.495
Extraversion	**5.323**	**0.025**	**6.873**	**0.012**	0.539	0.466
Excitement	0.289	0.594	0.277	0.601	0.684	0.412
Sulkiness	0.154	0.697	0.895	0.349	2.053	0.158
Anger/aggression	1.178	0.283	1.790	0.187	0.941	0.337
Anxiety	3.650	0.062	**6.750**	**0.012**	0.093	0.761
Depressiveness	**5.981**	**0.018**	2.579	0.115	0.533	0.469
Deactivation	1.101	0.299	0.016	0.901	0.889	0.351
Anhedonic reactivity	3.456	0.069	0.408	0.526	0.002	0.966
Introversion	**11.264**	**0.002**	0.505	0.481	0.073	0.789
Physical well-being/ indisposition	0.349	0.558	1.554	0.218	0.728	0.398
Positive feeling[a]	3.386	0.072	1.774	0.189	0.825	0.386
Negative feeling[b]	2.973	0.091	2.455	0.124	0.061	0.806

[a] Includes the scales relaxation, good mood and alertness

[b] Includes the scales excitement, sulkiness, anger, anxiety, depressiveness and deactivation

$0.0001 < p < 0.05$) with all of the RSSC scales, whereas negative correlations were found between participants' non-verbal behaviour and those BSKE-30 scales reflecting the negative mental state of feeling uncomfortable. For example, the scale 'Depressiveness' correlated significantly with all RSSC scales ($r = -0.50$ to -0.29, $0.0001 < p < 0.05$) and 'Introversion' with all but 'Duration of speech' and 'Conversational fluency' ($r = -0.45$ to -0.27, $0.001 < p < 0.05$).

Discussion

Social interaction in schizophrenia patients is often hampered by impairments in social cognition, in particular the correct processing and recognition of affective information non-verbally signalled by the conversational partner [56], as well as by impairments in spontaneous verbal [57] and non-verbal expressions [32, 58]. Thus, schizophrenia patients can be described and perceive themselves as being less socially skilled and socially competent than healthy persons [59–61], which constitutes an important source of stress for them [62] and often results in social withdrawal. According to the self-medication hypothesis, schizophrenia patients may consume nicotine in order to overcome their cognitive impairments and stress [6, 16]. Against this background, the present study aimed to test whether nicotine can also ameliorate social cognitive and social behavioural impairments in schizophrenia patients. It was expected that schizophrenia patients would perform worse in a facial affect recognition task and behave less competently and feel more uncomfortable during social interaction than healthy controls.

In contrast to our expectations and evidence repeatedly reported in the literature [29], our sample of schizophrenia patients did not perform significantly worse in the facial affect recognition task than the healthy controls. Thus, a precondition for showing performance-enhancing effects of nicotine in schizophrenia patients was not given, and accordingly, nicotine was not found to have a significant effect on facial affect recognition. A possible explanation for this unexpected absence of group differences between schizophrenia patients and healthy controls could be that the sample of patients consisted of clinically stable outpatients in a remitted state of the disease, who possibly had fewer social cognitive deficits than acute schizophrenia patients. This interpretation is in line with the results of a recent meta-analysis [29], which identified the inpatient/outpatient status as an important moderator variable for impairments in facial affect recognition and showed that inpatients were more impaired than outpatients or mixed groups of in- and outpatients. Another explanation for the absence of group differences in the affect recognition task might be the generally poor performance of the healthy control sample, which answered only 56 % of the age-discrimination task correctly, and only 72 % of the affect

recognition task. This was rather unexpected and differed considerably from the results of our former studies, in which healthy participants showed mean correct answer rates of 100 % [63, 64] and 83 % [65] in affect recognition tasks that used stimulus material comparable to that used in the present study. Besides the assumption that the age recognition task was too difficult to allow discrimination between groups, a possible explanation for the poor affect recognition performance might be the nicotine deprivation. Because of the study design, it is not possible to dissociate the effects of nicotine from the influence of nicotine deprivation on the participants' performance and we cannot automatically assume that the placebo condition reflects the 'baseline' performance in smokers. However, if nicotine deprivation did lead to a reduction in the performance of the healthy group, we would have expected an even greater reduction in the patients' performance, because the patients were stronger smokers and thus experienced a greater decrease in nicotine levels than the control sample. Hence, we should have found a group difference, but did not. The authors rather assume that the absence of a group difference is due to the circumstances of the measurements. The majority of the patients were familiar with fMRI measurements, since they are part of the diagnostic procedures in psychiatry. For most of the healthy participants, however, it was the first time that they experienced being inside an fMRI scanner; being in such a tight space may have caused such great discomfort that it reduced their concentration during the task. Another explanation might be that it was too difficult to discriminate between the chosen stimuli in the age recognition task.

The results regarding social competence in the role-play task corresponded with the hypothesis that schizophrenia patients are less socially skilled than healthy controls: schizophrenia patients showed a general reduction in expressive behaviour and scored worse in almost every subcomponent of non-verbal behaviour assessed by the rating scale. Although interrater agreement for the item 'Eye contact' was only fair despite an intensive rater training, the results for this item were consistent with the pattern of results for the other subcomponents. This pattern indicated a broad restriction in expressive behaviour in schizophrenia patients, which is usually interpreted as a lack of social competence during social interaction. As expected, the role-play task also induced a higher level of subjective stress in the schizophrenia patients than in the controls. These group differences in subjective feeling state and non-verbal behaviour during social interaction are in line with previous findings [19, 32, 35]. Thus, in contrast to facial affect recognition, the subjective stress level and social competence during social interaction showed the expected group differences between schizophrenia patients and healthy controls and both measures correlated with each other.

However, contrary to expectations derived from the self-medication hypothesis as well as from former studies showing relaxing effects of nicotine, at least in non-psychiatric smokers [10], nicotine did not have a relaxing effect on the subjective stress level in either of the groups. Nicotine only had effects on extraversion and anxiety and not on other measures such as subjective feeling state or non-verbal behaviour. In a study by Fidler and West [11], around 10 % of smokers stated 'aid to socializing' as a motive for smoking, and a meta-analytic review indicated that nicotine significantly increased vigour in smokers [66]. Feeling more extraverted would therefore fit the expectations. Nevertheless, our finding of only two single drug effects of nicotine does not seem very reliable when taking into account that two significant effects can be expected to occur by chance, given the number of subjective and behavioural variables assessed. Thus, we have to conclude that our study did not find any reliable nicotine effects or group-by-drug interactions in subjective well-being or social competence during the role-play.

The lack of nicotine effects might be a consequence of an inadequate dosage or time of testing after nicotine administration: the chosen dosage of 1 mg is comparable to one medium cigarette. Since the study sample—patients in particular—was rather heavy smokers and thus used to higher nicotine dosages, it seems possible that the dosage of nicotine was too low and that effects might have been more pronounced with higher dosages more comparable to the participants' usual consumption pattern. Also nicotine administration by spray is not identical to smoking a cigarette—thus, the possible (placebo) effects of context conditioning may have added to the lack of effects as well. Moreover, the interval between the administration of nicotine and the role-play task might have been too long. As the present experiment was embedded into a comprehensive study on nicotine effects using multiple tasks and concomitant fMRI and EEG recordings, the role-play took place almost 1 1/2 h after the drug administration. The half-life of nicotine administered by nasal spray is 2 h [67], that is, after 90 min, only about 65 % of the nicotine remains. This might be too little to cause effects measurable on the rating scales used.

On the other hand, if these technical explanations are not valid, the failure to find nicotine effects might also indicate that the self-medication hypothesis—which originated from nicotine effects on basic cognitive domains like attention and memory—cannot be transferred to domains such as social cognition and social behaviour. As impairments in these domains have been shown to have more impact than basic cognitive impairments on quality of life and functional outcome in schizophrenia patients [26, 68], such an interpretation would require a profound reconsideration of the self-medication hypothesis. Thus, the effects

of nicotine on social cognition on the one hand and on subjective stress level and social competence on the other should remain a focus of future research in schizophrenia.

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Conflict of interest None.

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