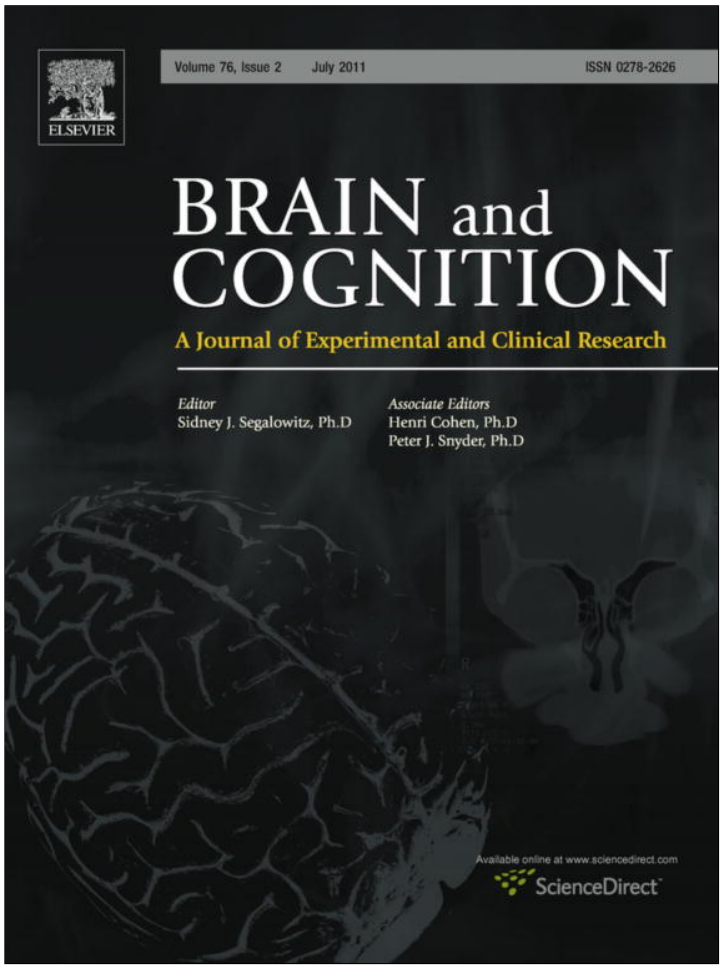

Brain and Cognition 76 (2011) 300–309

Contents lists available at ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Smoking reduces language lateralization: A dichotic listening study with control participants and schizophrenia patients

Constanze Hahn [a,*], Andres H. Neuhaus [b], Sakire Pogun [c], Michael Dettling [b], Sonja A. Kotz [d], Eric Hahn [b], Martin Brüne [a,e], Onur Güntürkün [a]

[a] Institute for Cognitive Neuroscience, Ruhr University Bochum, Bochum, Germany
[b] Department of Psychiatry and Psychotherapy, Charité University Medicine, Campus Benjamin Franklin, Berlin, Germany
[c] Center for Brain Research, Ege University, Izmir, Turkey
[d] Minerva Research Group 'Neurocognition of Rhythm in Communication', Max-Planck-Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[e] Research Department of Cognitive Neuropsychiatry and Psychiatric Preventive Medicine, LWL University Hospital, Ruhr-University Bochum, Bochum, Germany

ARTICLE INFO

Article history:
Available online 23 April 2011

Keywords:
Brain asymmetry
Language lateralization
Dichotic listening
Gender
Nicotine
Schizophrenia

ABSTRACT

Schizophrenia has been associated with deficits in functional brain lateralization. According to some authors, the reduction of asymmetry could even promote this psychosis. At the same time, schizophrenia is accompanied by a high prevalence of nicotine dependency compared to any other population. This association is very interesting, because sex-dependent effects of smoking in auditory language asymmetries have been reported recently, and the verbal domain is also one major focus in cognitive deficit studies of schizophrenia. Thus, the altered laterality pattern in schizophrenia could, at least in part, result from secondary artefacts due to smoking rather than being a pure cause of the disease itself. To test this hypothesis, the present study examined auditory language lateralization in 67 schizophrenia patients and in 72 healthy controls in a phonemic and an emotional dichotic listening task. Our findings replicate previous research, in that smoking reduces language lateralization in men in phonemic dichotic listening. In addition, we show that smoking also reduces laterality in women in the emotional dichotic listening task. Thus, smoking alters phonemic and emotional language asymmetries differentially for men and women, with a stronger effect for men in the left hemisphere phonemic task, and a stronger effect for women in the right hemisphere emotional task. Together, these findings point towards an effect of smoking which is possibly independent of sex and hemisphere. Importantly, by testing equal numbers of smoking and non-smoking patients and controls, we found no schizophrenia-associated asymmetry effect. Possible neurobiological mechanisms with which smoking may alter auditory microcircuits and thereby diminish left–right differences are discussed.

1. Introduction

Schizophrenia is a severe psychiatric disorder that affects about 1% of the population. Studies show that schizophrenia is associated with deficits of functional brain lateralization (Crow, 1997; Mitchell & Crow, 2005; Sommer, Aleman, Ramsey, Bouma, & Kahn, 2001). Sex differences and language deficits in the clinical symptomatology of schizophrenia are well established (reviewed in Flor-Henry, 1985; Wallentin, 2009); however, the neural mechanisms that produce these effects remain under debate. According to some authors (e.g., Crow, 2010) schizophrenia could even result from an altered asymmetry pattern.

Schizophrenia is also accompanied by an extremely high prevalence of nicotine dependency (Kumari & Postma, 2005; Ziedonis et al., 2008) and heavier smoking patterns (De Leon et al., 1995) compared to both the general population and other psychiatric disorders. Growing evidence points to neurobiological mechanisms underlying this significantly higher smoking prevalence. For example, converging evidence suggests that smoking modifies sensory gating deficits in schizophrenia, as well as increasing vigilance and attention (reviewed in Winterer, 2010). Based on several observations (e.g., Kumari & Postma, 2005), it has been proposed that smoking may be used as a self-medication by schizophrenic patients, because nicotine use has been found to transiently alleviate negative symptoms (Smith, Singh, Infante, Khandat, & Kloos, 2002) as well as cognitive impairments associated with the disorder (Adler, Hoffer, Wiser, & Freedman, 1993; Depatie et al., 2002; Kumari, Soni, & Sharma, 2001; Levin, Wilson, Rose, & McEvoy, 1996; Olincy, Ross, Young, Roath, & Freedman, 1998). These findings even extend to non-affected first-degree relatives

* Corresponding author. Address: Department of Biopsychology, Institute for Cognitive Neuroscience, Faculty of Psychology, Ruhr-University Bochum, GAFO 05/618, Universitätsstr. 150, D-44780 Bochum, Germany. Fax: +49 234 32 14377.
E-mail address: constanze.s.hahn@rub.de (C. Hahn).

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doi:10.1016/j.bandc.2011.03.015

of schizophrenia patients (Adler, Hoffer, Griffith, Waldo, & Freedman, 1992). Subsequent pharmacological challenge studies have further elucidated and characterized cognitive domains like attention and working memory targeted by nicotine consumption in schizophrenia (Harris et al., 2004; Sacco et al., 2005; Smith et al., 2006) and by nicotine exposure to non-smoking schizophrenia subjects (Barr et al., 2008), although challenge studies following smoking abstinence are likely confounded by withdrawal phenomena.

The confound of elevated smoking prevalence associated with its effects on cognition together with the notion of altered brain lateralization in schizophrenia is very interesting, because a recent study revealed sex-dependent effects of smoking in auditory language asymmetries (Hahn, Pogun, & Güntürkün, 2010). Using a consonant-vowel dichotic listening design in healthy adults, the authors showed that auditory language processing was adversely affected by smoking in men, which was accompanied by a decreased laterality index. In contrast, women remained unaffected by smoking. Further, a higher degree of lateralization was generally associated with a higher recognition rate on the dichotic listening task. Together, these findings argue for a greater vulnerability of the auditory system, and of auditory brain lateralization in particular, elicited by nicotine exposure in healthy male subjects. Notably, nicotine-mediated and sex-specific effects on laterality have been demonstrated in rats (Kanit, Koylu, Erdogan, & Pogun, 2005).

Sex differences have previously been observed in dichotic listening studies (Ikezawa et al., 2008; Meinschaefer, Hausmann, & Güntürkün, 1999; Wadnerkar, Whiteside, & Cowell, 2008), and fluctuations of sex hormones also elicit dynamic short-term changes in functional brain asymmetries (Bayer, Kessler, Güntürkün, & Hausmann, 2008; Bibawi, Cherry, & Hellige, 1995; Hausmann, Becker, Gather, & Güntürkün, 2002; Hausmann & Güntürkün, 2000; Heister, Landis, Regard, & Schroeder-Heister, 1989; Mead & Hampson, 1996; Rode, Wagner, & Güntürkün, 1995; Sanders & Wenmoth, 1998; Wadnerkar et al., 2008). Further differences between men and women also occur in various aspects of nicotine dependency and smoking habits (reviewed in Perkins, Jacobs, Sanders, & Caggiula, 2002; Pogun & Yararbas, 2009).

Importantly, the verbal domain, targeted by dichotic listening, is also one major focus of cognitive deficit studies of schizophrenia. In order to test the hypothesis that altered laterality might in fact result from secondary artefacts due to smoking rather than being a cause of the disease itself (Herzig, Tracy, Munafò, & Mohr, 2010), the present study examined auditory language lateralization of left and right hemisphere in smoking and non-smoking schizophrenic patients and healthy controls.

2. Method

2.1. Participants

Seventy-two (36 female) healthy adults (mean age = 34.35 ± 12.62 years) recruited via newspaper advertisements served as controls. All control subjects were examined by a psychiatrist before testing; only those without a history of psychiatric axis I disorder according to DSM-IV (American Psychiatric Association, 1994) or substance abuse (other than nicotine dependency) were included in the study. Severe medical or neurological condition, any psychopharmacological treatment or first-degree family history of psychiatric axis I disorder were additional exclusion criteria.

Sixty-seven (32 female) schizophrenia patients (mean age = 40.10 ± 11.18 years) participated in the study, and were recruited from the inpatient unit or the outpatient clinic of the Department of Psychiatry and Psychotherapy, Campus Benjamin Franklin, Charité University Medicine Berlin, Germany. Patients were included if they were diagnosed with schizophrenia according to DSM-IV and if they had no psychiatric disorder or substance abuse other than schizophrenia and nicotine dependency respectively. None of the patients had a history of severe medical disorder, severe neurological disorder, or electroconvulsive therapy. All patients received atypical or typical antipsychotic medication with a mean chlorpromazine (CPZ) equivalent of 564.90 ± 638.70 mg. Patients scored 12.28 ± 4.14, 14.67 ± 5.01, and 29.22 ± 7.18 in the Positive And Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) and were clinically stable. Mean duration of illness was 12.83 ± 11.32 years and mean number of episodes was 4.70 ± 4.55. Experimental patient groups were comparable with respect to these clinical characteristics; only non-smoking women had lower CPZ equivalents than smoking women ($F(1, 28) = 5.42$; $p = 0.027$; Cohen's $d = 0.88$; $\eta^2 = 0.16$). Clinical data of patients stratified by sex and smoking status are summarized in Table 1.

All participants reported normal or corrected-to-normal vision and were screened with audiometric testing at frequencies of 500, 1000, 1500, and 3000 Hz (MA25, MAICO Diagnostic GmbH) to ensure normal hearing in both ears. None of the participants had an interaural difference greater than 15 dB on any frequency. All participants were right-handed (handedness score >50), as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971, controls: mean EHI = 90.69 ± 18.89, patients: mean EHI = 86.59 ± 20.47; n.s.), and native-speakers of the German language. No differences with respect to handedness index occurred among any of the experimental groups.

With respect to age, patients were significantly older than controls ($F(1, 131) = 8.12$; $p = 0.005$; Cohen's $d = 0.48$; $\eta^2 = 0.06$) and across groups, women were older than men ($F(1, 131) = 5.71$; $p = 0.02$; Cohen's $d = 0.40$; $\eta^2 = 0.04$), but no age differences occurred within the patient and control subgroups. Nevertheless, age was included in the statistical analyses as a covariate, because age has been shown to affect brain lateralization (Beste, Hamm, & Hausmann, 2006; Gao, Boyd, Poon, & Clementz, 2007; Gootjes et al., 2006; Li, Moore, Tyner, & Hu, 2009; Obler, Woodward, & Albert, 1984).

Only participants who could be explicitly categorized as smokers or non-smokers were included in the study. To be considered a smoker, a participant had to smoke at least one cigarette per day and score at least one point on the German version of the Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991), i.e., Fagerström – Test für Nikotinabhängigkeit, FTNA; (Bleich, Havemann-Reinecke, & Kornhuber, 2002). A smoking history questionnaire queried year of smoking onset, number of cigarettes smoked per day, duration of nicotine dependence, and temporary smoking abstinence. Nicotine consumption was then quantified by cigarette pack years, calculated as packs smoked per day x years as a smoker, where 20 cigarettes = 1 pack. Non-smoking participants were defined as having consumed no more than 30 cigarettes in their lifetime. Smoking status and sex was counter-balanced across groups. Smoking groups did not differ with respect to age of smoking onset and amount of current daily cigarette consumption. However, patients had a higher Fagerström score ($F(1, 131) = 5.71$; $p = 0.02$; Cohen's $d = 0.58$; $\eta^2 = 0.09$) as well as more pack years ($F(1, 67) = 8.94$; $p = 0.004$; Cohen's $d = 0.71$; $\eta^2 = 0.12$) than controls, and female controls exhibited higher dependency scores than male controls ($F(1, 34) = 8.38$; $p = .007$; Cohen's $d = 0.96$; $\eta^2 = 0.20$). Demographic and smoking data of male and female controls and patients are provided in Table 2.

All subjects 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

Table 1
Demographic and Nicotine data of control participants and schizophrenic patients. Means (±S.D.) are provided for male and female smokers and non-smokers.

	Controls		Patients	
	Males	Females	Males	Females
Smokers				
N	*n* = 18	*n* = 18	*n* = 18	*n* = 17
Age (years)	31.50 ± 11.41	35.83 ± 12.13	38.39 ± 11.45	44.29 ± 11.36
Education (years)	14.78 ± 2.60	15.22 ± 1.77	13.67 ± 3.20	12.35 ± 2.32
EHI[a]	85.41 ± 15.23	89.54 ± 12.78	83.88 ± 20.99	92.14 ± 14.04
FTND[b]	3.67 ± 1.94	5.39 ± 1.61	5.61 ± 2.75	6.12 ± 2.52
Cigarettes per day	17.14 ± 7.40	19.86 ± 6.55	21.53 ± 11.51	22.24 ± 11.81
Smoking onset (age)	15.94 ± 1.89	15.22 ± 2.92	16.89 ± 6.14	16.53 ± 5.94
Nicotine (Pack Years)[c]	13.94 ± 12.67	17.43 ± 8.76	23.67 ± 17.49	28.74 ± 17.97
Non-smokers				
N	*n* = 18	*n* = 18	*n* = 17	*n* = 15
Age (years)	31.89 ± 13.13	38.17 ± 13.52	37.53 ± 11.37	40.33 ± 10.09
Education (years)	15.72 ± 3.23	16.17 ± 2.96	13.53 ± 3.86	16.67 ± 2.97
EHI	95.61 ± 28.53	92.21 ± 14.91	83.52 ± 27.48	87.05 ± 17.12

[a] EHI: Edingburgh Handedness Inventory assesses laterality index for handedness.
[b] FTND: Fagerström Test for Nicotine Dependency.
[C] One Pack Year: 20 cigarettes (=1 pack) smoked per day during 1 year.

Table 2
Clinical data of schizophrenia patients. Means (±S.D.) are provided for male and female smokers and non-smokers.

	Schizophrenia patients	
	Males	Females
Smokers		
DOI[a] (years)	14.44 ± 12.99	13.26 ± 10.87
Number of episodes	5.08 ± 4.38	5.13 ± 5.36
CPZ[b] equivalents (mg)	576.60 ± 768.67	754.56 ± 728.31
PANSS[c] positive scale	12.00 ± 2.97	12.56 ± 5.30
PANSS negative scale	15.18 ± 4.47	12.81 ± 4.04
PANSS general scale	30.73 ± 6.33	27.94 ± 6.25
Non-smokers		
DOI (years)	14.68 ± 12.31	8.71 ± 8.40
Number of episodes	5.00 ± 5.39	3.64 ± 3.00
CPZ equivalents (mg)	630.31 ± 598.31	274.86 ± 265.67
PANSS positive scale	13.13 ± 3.91	11.27 ± 3.85
PANSS negative scale	16.81 ± 5.64	14.00 ± 5.16
PANSS general scale	31.50 ± 8.58	27.07 ± 6.80

[a] DOI: duration of illness in years.
[b] CPZ: chlorpromazine.
[c] PANSS: Positive And Negative Syndrome Scale.

conducted in accordance with the Declaration of Helsinki and its amendments.

2.2. Dichotic listening tasks

Dichotic listening was assessed with a phonemic and an emotional task. In order to use the same stimulus material for both dichotic listening tasks, two-syllabic phonemic and emotional stimuli were used. Syllable sounds were recorded and validated by the Max-Planck-Institute for Human and Cognitive Brain Sciences in Leipzig, Germany. Thus, bi-syllabic sounds either elicited left or right hemisphere responses, depending on the task.

2.2.1. Phonemic dichotic listening task

Five doubled consonant–vowel (CV) syllables, "*baba*", "*dada*", "*fafa*", "*lala*", and "*tata*", spoken by a female speaker in a neutral tone of voice, served as stimuli. Two types of trials can be distinguished: On dichotic trials, the ears simultaneously received different stimuli, while on diotic trials (homonyms), the same stimulus was delivered to both ears. The stimuli were matched in volume and voice-onset-time (VOT) and were standardized for length. This was performed for each syllable-pair by matching the spectral temporal envelopes of the syllables and by controlling for differences between VOT of voiced (e.g., "gaga") and voiceless (e.g., "tata") stop-consonants. All possible combinations of the CV pairs were applied to both ears, thus cancelling out potentially confounding effect of VOT-induced variability. An Inter-Stimulus-Interval (ISI) of 3 s followed playback of each stimulus pair, during which time participants indicated by key press which stimuli they had perceived. For this purpose, a five-button response-box, built by the Psychology workshop of the Ruhr University Bochum, Germany, was used, each button labeled with the respective syllable. Participants were instructed to answer as accurately and as quickly as possible, even if they were not sure about the response. One hundred and twenty-five trials were administered, divided into five blocks of 25 trials each, with short breaks between each block. Every block contained all 25 possible syllable permutations in random order. The task was preceded by 20 practice trials divided into two blocks of 10 trials. Primary outcome variables were the numbers of correctly identified dichotic stimuli attributable to each ear and the corresponding reaction times. In addition, a dichotic laterality index (Li) was calculated as follows:

$$\mathrm{LI} = \frac{\text{Correct right ear responses} - \text{Correct left ear responses}}{\text{Correct right ear responses} + \text{Correct left ear responses}} \times 100$$

The LI by definition varies between −100 and +100, with positive values indicating that more stimuli were identified by the right ear (right ear advantage; REA), and negative values correspondingly indicating left ear advantage (LEA).

2.2.2. Emotional dichotic listening task

This task was designed to measure auditory functional asymmetry with respect to emotional prosody. Apart from stimuli intonation, the task was identical to the phonemic dichotic listening task. Only one syllable, "*dada*", was used, but spoken in five different emotional intonations: *happy*, *sad*, *neutral*, *angry*, and *surprised*. The stimuli were spoken by the same female speaker as in the phonemic dichotic listening task, matched in volume,

voice-onset-time, and standardized for length. Participants were asked to indicate by key press which emotion they had perceived. The response buttons were labeled with emoticons corresponding to the five emotions. Emoticons were simple cartoon drawings of five faces for each emotion, and they were used instead of spelled-out words to avoid any interference with phonetic stimulation (Voyer, Bowes, & Soraggi, 2009). Primary outcome variables were equivalent to those of the phonemic dichotic listening task, i.e., laterality index, left and right ear responses and reaction times.

2.3. Procedure

The experiment was carried out in a windowless, brightly lit, and quiet laboratory room. In order to minimize environmental influences during the experiment, a symmetrically arranged experimental box of approximately 1.5 × 1.5 m, open rearwards and towards the top, was separated from the room by movable walls. Participants at inside the box, a customary Personal Computer (with AMD Duron 1.3 GHz CPU, 512 MB RAM) was placed underneath a table. Responses were collected via a standard PS/2 keyboard enclosed by a five-button response box (Psychology workshop, Ruhr University Bochum, Germany). Standardized instructions for the tasks were provided by the experimenter verbally, in a written form, and also displayed on the monitor for computer tasks. In order to avoid response hand effects, response hands were switched during each break within the tasks. Start hand for each task was counter-balanced across participants. The index finger was used for all responses. During practice trials, the experimenter observed the participant and clarified instructions if necessary. Task order was counterbalanced.

2.4. Statistical analysis

SPSS 14.0 (SPSS Inc., USA) was used for statistical analysis. LI as dependent variable was analyzed in a 2 (patient vs. control) × 2 (smoker vs. non-smoker) × 2 (male vs. female) ANCOVA with age as a covariate. Analyses of number of correct stimulus identifications and mean reaction times as dependent variables additionally included the factor ear (left vs. right) as a within-subject factor, resulting in a 2 × 2 × 2 × 2 repeated measures ANCOVA, again with age as a covariate. No differences occurred between right hand and left hand responses or with respect to headphone switch, thus, all test responses were collapsed for subsequent analyses. Demographic and clinical data were analyzed with *t*-tests for independent samples. For all tests of significance, a two-tailed alpha–level of $p < 0.05$ was used. Significant effects were further examined by post hoc analyses with Bonferroni correction.

2.5. Outlier exclusion and missing data

Outlier identification procedures were performed for the dichotic listening tasks and for each participant individually. A reaction time was excluded from analyses if it fell below 100 ms (anticipation errors) or exceeded the participant's mean reaction time in the task by more than three standard deviations. Iterations of this algorithm were applied until no further outliers were yielded. The mean number of reaction time outliers across tasks was 1.68 (S.D. = 1.00). Thereafter, outliers regarding mean accuracy were identified. This was achieved by subtracting each participant's number of correct dichotic responses from the mean number of correct dichotic responses of all participants. If this difference exceeded three standard deviations, the respective task was labeled as an outlier for this individual participant and disregarded. No accuracy outliers were found.

3. Results

3.1. Validity of dichotic listening tasks

The mean (±S.D.) laterality index of all 139 participants for phonemic dichotic listening was 41.86 (±43.80), indicating significant lateralization to the left speech dominant hemisphere ($t(138) = 11.27$; $p < 0.001$; 95% *CI* [34.51, 49.20]). More stimuli were correctly identified by the right ear ($M = 69.48$ (±21.74)) than by the left ear ($M = 28.47$ (±21.58); $t(138) = 11.19$; $p < 0.001$; Cohen's $d = 1.89$), and stimuli perceived by the right ear ($M = 1330.99$ ms (±223.98)) were responded to faster than those detected by the left ear ($M = 1476.40$ ms (±282.09); $t(134) = -8.60$; $p < 0.001$; Cohen's $d = 0.57$).

The overall mean laterality index for emotional dichotic listening was −10.13 (±36.33); $p = 0.01$; 95% *CI* [−16.27, −3.99]) with more stimuli correctly identified by the left ear ($M = 40.51$ (±16.78)) than by the right ear ($M = 33.54$ (±17.62); $t(138) = 2.70$; $p = 0.08$; Cohen's $d = 0.41$). Also, stimuli were responded to faster when recognized by the left ear ($M = 1575.79$ ms (±253.49)) than by the right ear ($M = 1616.99$ ms (±273.94); $t(137) = -2.51$; $p = 0.013$; Cohen's $d = 0.16$). Thus, emotional dichotic stimuli lateralized toward the right hemisphere, although degree of lateralization was stronger in the phonemic dichotic listening task ($t(138) = 8.54$, $p < 0.001$; Cohen's $d = 0.79$). Overall, emotional dichotic listening was more difficult, as it elicited fewer number of correct choices ($M = 74.58$ (±15.01) vs. $M = 98.00$ (±3.12); $t(137) = 19.59$; $p < 0.001$; Cohen's $d = 2.16$), and slower reaction times compared to phonemic dichotic listening ($M = 1399.68$ ms (±234.32) vs. $M = 1598.50$ ms (±247.35); $t(133) = -10.00$; $p < 0.001$; Cohen's $d = 0.83$).

3.2. Phonemic dichotic listening

A 2 (patient vs. control) × 2 (smoker vs. non-smoker) × 2 (male vs. female) ANCOVA with age as covariate revealed a significant smoking *sex interaction effect on LI ($F(1, 130) = 8.13$; $p = 0.005$; $\eta^2 = 0.06$; see Fig. 1 and Table 3). No other main and interaction effects on LI were observed, thus controls and patients did not differ with respect to phonemic language lateralization. Post hoc tests revealed that non-smoking men ($M = 55.82$ (±41.67) had significantly higher LIs than smoking men ($M = 35.36$ (±36.87); $F(1, 68) = 4.98$; $p = 0.031$; Cohen's $d = 0.52$; $\eta^2 = 0.07$), and they also had higher LIs than non-smoking women ($M = 27.47$ (±49.24); $F(1, 65) = 5.35$; $p = 0.024$; Cohen's $d = 0.62$; $\eta^2 = 0.07$).

Using ear (left vs. right) as within-subject factor, and group, smoking status, and sex as between-subjects factors, correct

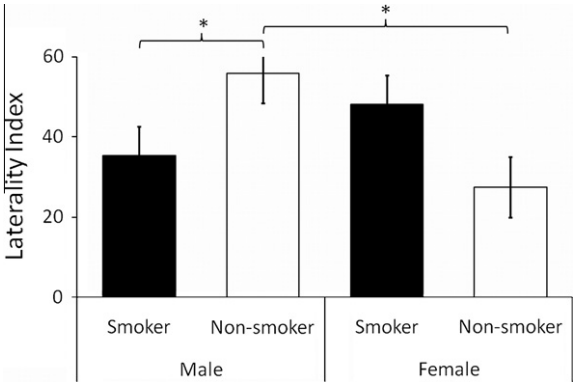

Fig. 1. Laterality index of the phonemic dichotic listening task for male (left) and female (right) participants stratified by smokers (black) and non-smokers (white) (*$p < 0.05$). Smoking men were less lateralized to the left hemisphere than non-smoking men, while no significant difference occurred in women.

Table 3
Phonemic dichotic listening task: means and standard deviations of each experimental group for number of right ear and left ear responses, and laterality index.

	Controls		Patients	
	Males	Females	Males	Females
Smokers				
RE	62.72 ± 19.03	72.72 ± 24.43	68.28 ± 16.08	72.94 ± 19.43
LE	36.06 ± 19.33	26.06 ± 23.83	27.11 ± 16.87	24.59 ± 18.73
LI	27.11 ± 38.68	46.97 ± 48.85	43.60 ± 34.03	49.37 ± 56.97
Non-smokers				
RE	76.67 ± 24.25	66.89 ± 21.12	76.65 ± 18.00	57.60 ± 27.29
LE	22.72 ± 24.49	32.22 ± 20.67	20.41 ± 16.00	39.80 ± 27.95
LI	54.39 ± 49.01	34.80 ± 42.02	57.33 ± 33.66	18.68 ± 56.97

RE: right ear responses are dichotic stimuli correctly identified on the right ear channel.
LE: left ear responses are dichotic stimuli correctly identified on the left ear channel.
LI: laterality index calculated for dichotic stimuli correctly identified on either ear.

stimulus identifications were analyzed in a repeated measures ANCOVA with age as covariate. This $2 \times 2 \times 2 \times 2$ model revealed a significant main effect of group ($F(1, 130) = 18.58$; $p < 0.001$; $\eta^2 = 0.13$) in that controls were able to identify more stimuli correctly ($M = 99.01$ (±1.07) than patients ($M = 98.81$ (±4.15)). No significant between subject interaction occurred.

Within-subject analyses revealed a three-way ear∗smoker∗sex interaction ($F(1, 130) = 8.58$, $p = 0.004$; $\eta^2 = 0.06$), hence a sex-specific and smoking-dependent effect of ears unrelated to diagnostic group. A 2 (smoking) × 2 (sex) post hoc ANCOVA for right ear choices revealed a sex∗smoking interaction ($F(1, 134) = 9.68$, $p = 0.004$; $\eta^2 = 0.06$) with non-smoking men ($M = 76.66$ (±21.13) having more right ear responses than smoking men ($M = 65.50$ (±17.59); $F(1, 68) = 5.93$; $p = 0.018$; Cohen's $d = 0.57$; $\eta^2 = 0.08$), and non-smoking men also had more right ear responses than non-smoking women ($M = 62.87$ (±24.18); $F(1, 65) = 5.25$; $p = 0.025$; Cohen's $d = 0.61$; $\eta^2 = 0.08$). A post hoc ANCOVA for left ear choices also revealed a sex∗smoking interaction ($F(1, 134) = 7.96$, $p = 0.006$; $\eta^2 = 0.06$), however, in the opposite direction, with smoking men having more left ear responses ($M = 31.58$ (±16.45)) than non-smoking men ($M = 21.60$ (±20.53); $F(1, 68) = 4.71$; $p = 0.033$; Cohen's $d = 0.54$; $\eta^2 = 0.07$), and non-smoking men also detecting fewer left ear responses than non-smoking women ($M = 35.67$ (±24.16); $F(1, 65) = 5.47$; $p = 0.022$; Cohen's $d = 0.63$; $\eta^2 = 0.08$).

Analysis of reaction times (see Table 4) was conducted with the same $2 \times 2 \times 2 \times 2$ ANCOVA, entering ear (left vs. right) as within-subject factor, group (patient vs. control), smoking status (smoker vs. non-smoker), and sex (male vs. female) as between-subjects factors, and age as covariate. This general linear model revealed the following between subject effects: (a) a main effect of group ($F(1, 126) = 11.58$; $p = 0.001$; Cohen's $d = 0.73$; $\eta^2 = 0.08$) in that controls responded faster to stimuli ($M = 1326$ ms (±203)) than patients ($M = 1487$ ms (±239)); (b) a main effect of smoking ($F(1, 126) = 5.10$; $p = 0.026$; Cohen's $d = 0.34$; $\eta^2 = 0.04$) with smokers ($M = 1443$ ms (±247)) exhibiting slower response times than non-smokers ($M = 1363$ ms (± 216)); (c) a main effect of sex ($F(1, 126) = 6.02$; $p = 0.016$; Cohen's $d = 0.30$; $\eta^2 = 0.05$) in that women ($M = 1367$ ms (±235) responded faster than men ($M = 1438$ ms (±231)); and (d) a group∗smoking interaction ($F(1, 126) = 4.15$; $p = 0.044$; $\eta^2 = 0.03$) where only smoking patients had slower reaction times than non-smokers ($F(1, 65) = 7.87$; $p = 0.007$; Cohen's $d = 0.72$; $\eta^2 = 0.11$), and only within the smoking group did patients differ from controls ($F(1, 66) = 15.18$; $p < 0.001$; Cohen's $d = 1.15$; $\eta^2 = 0.19$).

Correlation analysis revealed that patients' duration of illness was associated with higher LI in phonemic dichotic listening ($N = 67$; r = 0.348; $p = 0.008$.), and, symptom severity of schizophrenia (PANSS) was associated with more RE choices ($N = 67$; $r = 0.269$; $p = 0.043$).

Table 4
Phonemic dichotic listening task: means and standard deviations of reaction times (in ms) for each experimental group for right ear and left ear responses.

	Controls		Patients	
	Males	Females	Males	Females
Smokers				
RE (ms)	1323 ± 178	1208 ± 160	1503 ± 241	1476 ± 180
LE (ms)	1478 ± 308	1305 ± 197	1631 ± 267	1661 ± 298
Non-smokers				
RE (ms)	1252 ± 150	1251 ± 210	1329 ± 211	1318 ± 292
LE (ms)	1407 ± 244	1382 ± 266	1566 ± 279	1394 ± 216

RE: right ear responses are dichotic stimuli correctly identified on the right ear channel.
LE: left ear responses are dichotic stimuli correctly identified on the left ear channel.

3.3. Emotional dichotic listening

A 2 (patient vs. control) × 2 (smoker vs. non-smoker) × 2 (male vs. female) ANCOVA with age as covariate revealed a significant two-way smoking∗sex interaction effect on LI ($F(1, 130) = 4.66$; $p = 0.03$; $\eta^2 = 0.04$; see Fig. 2 and Table 5). No other effects were significant that differentiated patients from controls. Post hoc ANCOVAs revealed that non-smoking women ($M = -22.07$ (±38.57)) were stronger lateralized to the right hemisphere than smoking women ($M = -3.30$ (±36.36); ($F(1, 64) = 4.94$; $p = 0.030$; Cohen's $d = 050$; $\eta^2 = 0.07$). No significant effects were found in male participants.

Correct stimulus identifications were analyzed in a $2 \times 2 \times 2 \times 2$ repeated measures ANCOVA that revealed a significant main effect of group ($F(1, 130) = 38.69$; $p < 0.001$; Cohen's $d = 1.06$; $\eta^2 = 0.23$), indicating that controls correctly identified more stimuli ($M = 81.44$ (±11.57) than patients ($M = 65.97$ (±16.98)). Also, a main effect of sex was found $F(1, 128) = 7.34$; $p = 0.008$; Cohen's $d = 0.20$; $\eta^2 = 0.05$), as women ($M = 75.71$ (±17.21)) identified more stimuli correctly than men ($M = 72.43$ (±15.36)).

Within-subject analyses again revealed a three-way ear∗smoker∗sex interaction ($F(1, 128) = 5.06$, $p = 0.026$; $\eta^2 = 0.04$) unrelated to diagnostic group. Considering right ear choices, a post hoc ANCOVA revealed a smoking∗sex interaction ($F(1, 132) = 5.01$; $p = 0.027$; $\eta^2 = 0.04$). Although non-smoking women tended to have the lowest number of correct choices, this comparison did not reach significance. Analysis of left ear choices yielded a smoking∗sex interaction ($F(1, 132) = 3.87$; $p = 0.05$; $\eta^2 = 0.03$) with non-smoking women having more LE responses ($M = 48.18$ (±18.27)) than non-smoking men ($M = 37.97$ (±16.39); $F(1, 64) = 5.27$; $p = 0.025$; Cohen's $d = 0.59$; $\eta^2 = 0.08$)).

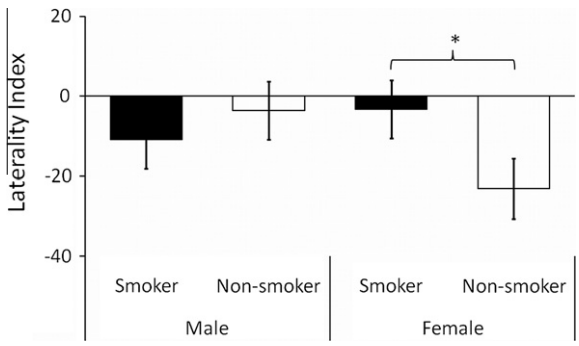

Fig. 2. Laterality index of the emotional dichotic listening task for male (left) and female (right) participants stratified by smokers (black) and non-smokers (white) ($^*p < 0.05$). Smoking women were less lateralized to the right hemisphere than non-smoking women, while no significant difference occurred in men.

Table 5
Emotional dichotic listening task: means and standard deviations of each experimental group for number of right ear and left ear responses, and laterality index.

	Controls		Patients	
	Males	Females	Males	Females
Smokers				
RE	34.61 ± 15.27	42.28 ± 16.63	28.06 ± 12.07	29.88 ± 20.89
LE	42.89 ± 15.47	41.22 ± 15.61	35.11 ± 12.59	33.12 ± 16.53
LI	−10.67 ± 34.52	0.62 ± 36.37	−11.15 ± 25.55	−7.71 ± 37.01
Non-smokers				
RE	43.44 ± 24.36	31.67 ± 15.75	29.06 ± 7.73	27.60 ± 17.65
LE	39.33 ± 19.44	50.33 ± 17.57	36.44 ± 12.56	45.60 ± 19.38
LI	1.87 ± 48.53	−22.23 ± 37.55	−9.71 ± 21.85	−24 08 ± 41.07

RE: right ear responses are dichotic stimuli correctly identified on the right ear channel.
LE: left ear responses are dichotic stimuli correctly identified on the left ear channel.
LI: laterality index calculated for dichotic stimuli correctly identified on either ear.

The $2 \times 2 \times 2 \times 2$ repeated measures ANCOVA revealed a significant main effect of group on reaction times ($F(1, 128) = 3.99$; $p = 0.048$; Cohen's $d = 0.42$; $\eta^2 = 0.03$). Controls responded faster to correct stimuli ($M = 1548$ (±231)) than patients ($M = 1650$ (±253)). Also, a main effect of sex was found ($F(1, 128) = 5.51$; Cohen's $d = 0.37$; $p = 0.02$; $\eta^2 = 0.04$) where women ($M = 1550$ (±231)) responded faster than men ($M = 1640$ (±253), see Table 6).

4. Discussion

4.1. Validity of tasks

This study employed two new dichotic listening tasks to examine sex-specific effects of smoking on left and right hemisphere language lateralization in schizophrenia patients and healthy controls. In this context, we created and validated new bi-syllabic stimuli, which elicit contrasting lateralization patterns based on the instruction to focus on phonemic or emotional information, respectively. In addition, reaction times were calculated. Monosyllabic consonant–vowel-consonant sounds are commonly used in phonemic dichotic listening tasks (Bayazit, Öniz, Hahn, Güntürkün, & Ozgoren, 2009; Berlin, Lowe-Bell, Cullen, & Thompson, 1973; Hugdahl et al., 2008; Penna et al., 2007; Sandmann et al., 2007). Occasionally, rhyming words are also used for the same purpose in the fused dichotic words test (Asbjørnsen & Bryden, 1996). For emotional dichotic listening paradigms, bi-syllabic stimuli have been established in several studies (e.g., Bryden & MacRae, 1988; Buchanan et al., 2000; Voyer et al., 2009). These identical bi-syllabic words additionally served as the phonemic condition in these studies, and they actually proved to be at least as reliable as the traditional monosyllabic stimuli (Russell & Voyer, 2004). Our study also used identical bi-syllabic sounds in phonemic and emotional condition; moreover, our stimuli were free from any semantic meaning. Importantly, we could show that both dichotic listening tasks serve as valid tools to assess hemispheric language lateralization, and although the degree of lateralization in the emotional condition was smaller than in the phonemic condition, the phonemic task elicited comparable mean LIs and correctly identified ear responses compared to our previous study (Hahn et al., 2010).

Table 6
Emotional dichotic listening task: means and standard deviations of reaction times (in ms) for each experimental group for right ear and left ear responses.

	Controls		Patients	
	Males	Females	Males	Females
Smokers				
RE (ms)	1566 ± 227	1518 ± 312	1832 ± 259	1577 ± 238
LE (ms)	1575 ± 219	1449 ± 278	1732 ± 197	1615 ± 251
Non-smokers				
RE (ms)	1625 ± 243	1555 ± 233	1603 ± 332	1661 ± 264
LE (ms)	1608 ± 254	1489 ± 176	1569 ± 322	1572 ± 248

RE: right ear responses are dichotic stimuli correctly identified on the right ear channel.
LE: left ear responses are dichotic stimuli correctly identified on the left ear channel.

4.2. Smoking affects laterality

In accordance to previous research (Hahn et al., 2010) the phonemic task revealed that smoking men had lower LI than non-smoking men. This was caused by a dramatically reduced RE advantage accompanied with only slightly increased LE responses. At the same time, women were not adversely affected by smoking in this paradigm. Hahn et al. (2010) proposed a model for their findings that departs from the fact that smoking, especially when starting early and consuming excessive quantities over extended periods of time, is known to cause axonal damages to the ascending thalamocortical fibers that transfer auditory verbal input (Jacobsen, Picciotto et al., 2007; Kawai, Lazar, & Metherate, 2007). Structural impairments of the thalamocortical system reduce right ear advantage and thus decrease the laterality index (Jacobsen, Slotkin, Mencl, Frost, & Pugh, 2007). These damages are more pronounced in males than in females, and males are more vulnerable at already lower levels of nicotine (Slotkin et al., 2007). The absence of a similar deficit in women was interpreted by Hahn et al. (2010) as resulting from sex-specific hormonal conditions that could exert neuroprotective effects (Vagnerova, Koerner, & Hurn, 2008). Indeed, progesterone reduces the expression of proinfammatory genes (Dubal, Shughrue, Wilson, Merchenthaler, & Wise, 1999) and neuronal degeneration (Marques-Vidal, Sie, Cambou, Chap, & Perret, 1995), while at the same time facilitating neuronal repair mechanisms (Morali et al., 2005).

We now have to extend and alter this model, as we found a highly similar pattern in the emotional dichotic listening task, but this time only for women. Thus, although smoking indeed reduces phonemic and emotional language asymmetries in a sex-specific way, this effect is stronger for men in the left hemisphere phonemic and stronger for women in the right hemispheric emotional task. This makes it unlikely that the absence of a smoking-effect in the phonemic task in women is due to the neuroprotective effects of progesterone, otherwise it would be expected that women would also be unaffected in the emotional task. As outlined below, an important alternate explanation seems more likely: smoking alters language asymmetries, independent of sex and hemisphere.

Although nicotine is the major addictive component of tobacco, other components, such as monoamine oxidase inhibitors, acetaldehyde and ammonia may also modulate the reinforcing effects of nicotine and impact smoking behavior (Rose, 2006). However, in schizophrenia patients, the central effects of nicotine appear to play a central role in tobacco addiction (Kumari & Postma, 2005; Leonard, Mexal, & Freedman, 2007; Leonard et al., 1996). Binding of nicotine to nicotinic acetylcholine receptors exerts predominantly modulatory effects on cellular excitability (Wonnacott, Sihpuara, & Balfour, 2005). These receptors are abundant within the white matter of ascending auditory thalamocortical fibers, and their activation results in increased axonal excitability (Kawai et al., 2007). Consequently, nicotine lowers the threshold for auditory thalamocortical transmission at an early stage of processing, thereby increasing the probability for soft signals to activate cortical responses by regulating cortical signal-to-noise levels (Alkondon, Perira, Eisenberg, & Albuqerque, 2000; Rudnick, Koehler, Picciotto, & Siegel, 2009). If nicotine indeed modulates early auditory processes, it would affect a major mechanism of language asymmetry. Dichotic listening studies with phonemic tasks show that the right ear advantage results to a great extent from a bottom-up attentional bias towards the dominant ear (Hugdahl et al., 2009). The same is found for lateralized word processing in the visual modality (Nicholls, Wood, & Hayes, 2001). Taken together, chronic nicotine exposure reduces perceptual asymmetries, since it pathologically alters ascending auditory microcircuitry during development (Liang et al., 2006), thereby possibly altering the threshold for thalamocortical transmission. Indeed, in the present study, nicotine overall reduced asymmetries in the phonemic (left hemisphere) and in the emotional (right hemisphere) task. However, asymmetry was pronounced for the phonemic task in men and for the emotional task in women. If smoking reduces asymmetries in an overall manner, it is therefore inevitable to find higher LI-values for non-smoking men in the phonemic and for non-smoking women in the emotional task.

4.3. Language laterality in schizophrenia

With respect to asymmetry patterns, we found no difference between schizophrenia patients and controls. Thus, the relative contribution of left and right ear choices did not differ between the two groups, although controls consistently outperformed patients on both dichotic listening tasks with respect to correct responses and reaction times. At first glance, these findings seem to contradict one well established view, according to which altered lateralization may be one core characteristic of schizophrenia (Crow, 1997, 2010; Mitchell & Crow, 2005; Sommer, Aleman, Ramsey, Bouma, & Kahn, 2001). However, while lower response accuracy and higher response latencies reflect a commonly reported finding in schizophrenia, dichotic listening studies have in fact continuously yielded controversial results with respect to LI. Indeed, a large number of studies have revealed reduced lateralization in schizophrenia (e.g., Bleich-Cohen, Hendler, Kotler, & Strous, 2009; Løberg, Hugdahl, & Green, 1999; Rhinewine & Docherty, 2002; Romney & Addington, 2000; Sakuma, Hoff, & DeLisi, 1996). However, a substantial body of research has also found no laterality differences (e.g., Carr, Waleb, Dewisa, & Stephan, 1992; Collinson, Mackay, James, & Crow, 2009; Gruzelier & Hammond, 1980; Hatta, Yamamoto, & Kawabata, 1984; Løberg, Jørgensen, & Hugdahl, 2002; Raine, Andrews, Sheard, Walder, & Manders, 1989; Yozawitz et al., 1979; Øie, Rund, Sundet, & Bryhn, 1998), and a few studies have even shown increased laterality in schizophrenia patients (Lerner, Nachshon, & Carmon, 1977; Lishman, Toone, Colbourn, McMeekan, & Mance, 1978; Walker & McGuire, 1982). Recently, these contrasting findings appear to be partially reconciled by more closely examining factors associated with schizophrenia, for instance, positive and negative symptom severity as well as duration of illness (Carr et al., 1992; Collinson et al., 2009; Løberg et al., 2006; Øie, Sundet, & Ueland, 2011). These recent findings also conform to our detected associative findings, thus lending support to the idea that altered functional lateralization in schizophrenia may reflect a variable state, dependent on the individual course of the disorder rather than entirely reflecting a preset condition in the brain (Collinson et al., 2009).

The progression of the disease is different in male and female schizophrenia patients. Female patients require lower doses of neuroleptic medication than male patients (Salokangas, 1995, 2004; Seeman, 1986). In the current study, medication intake (CPZ equivalents in mg) was lowest in non-smoking females and lower compared to smoking female patients. In clinical practice, the dose of antipsychotic medication is decreased when schizophrenia patients stop or reduce smoking (Šagud et al., 2009). Smoking stimulates the cytochrome (CYP) isozymes and has significant impact on the pharmacodynamics of antipsychotic medication (reviewed in Desai, Seabolt, & Jann, 2001). There are sex differences in response to antipsychotic drugs with women requiring lower doses than men (reviewed in Pogun & Yararbas, 2010). CYP2A6 and CYP2B6 activities are higher in women than men (Mwenifumbo & Tyndale, 2009). High CYP2A6 activity is associated with fast metabolism, which is further related to high nicotine dependence (Tyndale & Sellers, 2002). Subsequently, higher nicotine metabolism in female smokers is likely to be the case in the current study. Non-smoking female patients require less medication and they have more years of education (in fact, most years of education across the whole sample). A later onset of illness compared to smoking female patients does not seem to be the case, given comparable results for age minus DOI. On the other hand, genetic association between schizophrenia and smoking may also be considered (Faraone et al., 2004). In our study, PANSS scores argue against deviant symptom severity, and medication intake was uncorrelated to LIs. In addition, our finding that smoking significantly modulated LIs of phonemic and emotional dichotic listening of patients and of control participants in the very same way, strongly argues for the important role of smoking to drive laterality changes.

Apart from factors related to sex, smoking prevalence is also related to many other factors, including but not limited to socioeconomic status (Carroll, Anker, & Perry, 2009; Johnson & Novak, 2009). Similarly, measures of socioeconomic status have indicated elevated risk for schizophrenia onset among people with less socioeconomic security (Gallagher, Jones, McFalls, & Pisa, 2006). Although it is clear that socioeconomic status – and also many other variables – are associated with tobacco use and schizophrenia disorder, these environmental factors likely do not contribute to elucidating the detected association between smoking and language lateralization in the current study.

According to our research, smoking constitutes another key factor to influence language lateralization. We previously reported a strong impact of smoking on LI in healthy participants (Hahn et al., 2010), and now reveal a virtually identical pattern extending to schizophrenia patients. This is an important finding, because traditionally, studies of schizophrenia patients do not account for the unequal proportion of smokers and non-smokers within experimental groups (Kumari & Postma, 2005). Consequently, the average empirical study is likely biased towards comparing non-smoking (male) controls with smoking (male) patients, which – in light of our current findings – would inevitably yield reduced language lateralization in patients compared to controls. Indeed, when interpreting the absence of asymmetry differences between groups in our study, it is important to emphasize that we tested equal amounts of smoking and non-smoking patients and controls. Thus, the absence of a schizophrenia-associated asymmetry-effect

in our data set goes along with our strategy to control for smoking habits in our subjects.

5. Conclusion

We contribute two main findings. First, we show that smoking reduces functional language asymmetries. This is (possibly) independent of sex, and also of the language system under study: it applies in a similar way to a left hemispheric process of phonemic discrimination and a right hemispheric function of prosodic recognition. The mechanisms with which smoking alters auditory microcircuits and thereby diminishes left–right differences can presently only vaguely be inferred. The second main finding is the complete absence of an asymmetry-related difference between patients and controls. Although negative findings should be interpreted with the greatest of care, we are inclined to believe that our strategy to control for smoking contributed to this result. Previous studies failed to account for different smoking prevalence between groups in the context of brain lateralization – and beyond. Ultimately, some of the controversies around altered language lateralization in schizophrenia may be reconciled by accounting and controlling for cigarette smoking.

6. Conflict of interest

None declared.

Acknowledgments

This research was supported by the DFG research Grant (Gu227/12) and by the DAAD PhD-Net Grant. For assistance with data collection, we would like to thank Miriam Biene and Jonas Lins, and we thank Osman Iyilikci for his help with task programming. The authors thank all participants of this study for contributing their time and effort. C.H. was supported by the International Graduate School of Neuroscience fellowship, the Ruhr-University Bochum Rectorate fund, and the ''Studienstiftung des deutschen Volkes'' (German National Scholarship Foundation). This study is part of the PhD dissertation of C.H. and has been recognized by an NCI SRNT travel award to be presented at the 17th annual SRNT-Meeting in Toronto, February 16–19, 2011.

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