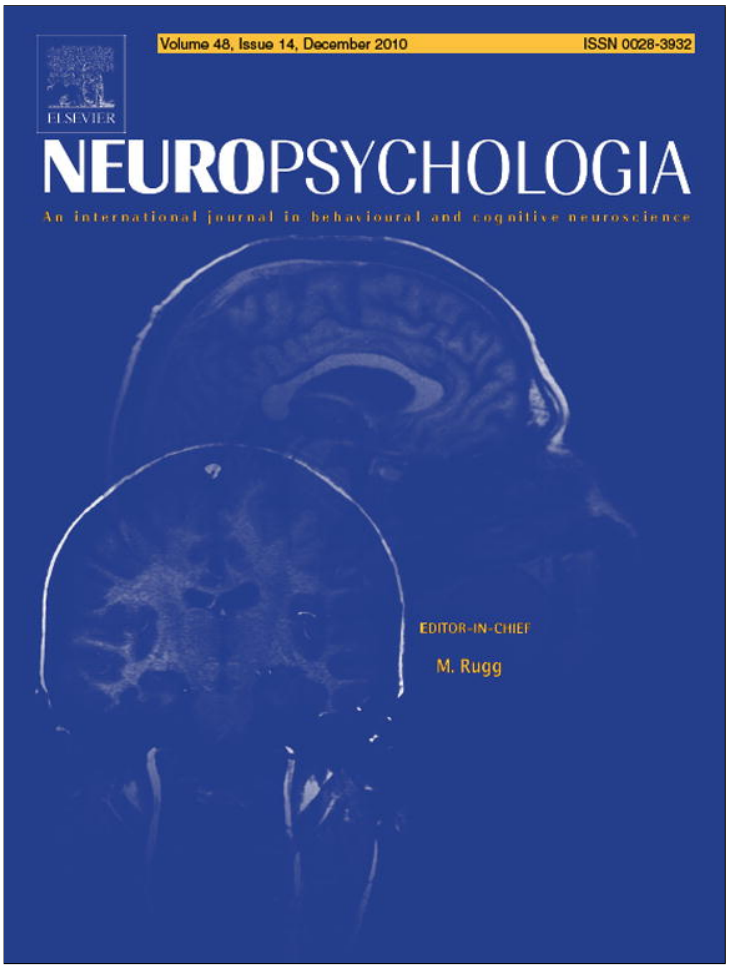

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Smoking modulates language lateralization in a sex-specific way

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ABSTRACT

Smoking affects a widespread network of neuronal functions by altering the properties of acetylcholinergic transmission. Recent studies show that nicotine consumption affects ascending auditory pathways and alters auditory attention, particularly in men. Here we show that smoking affects language lateralization in a sex-specific way. We assessed brain asymmetries of 90 healthy, right-handed participants using a classic consonant–vowel syllable dichotic listening paradigm in a 2 × 3 experimental design with sex (male, female) and smoking status (non-smoker, light smoker, heavy smoker) as between-subject factors. Our results revealed that male smokers had a significantly less lateralized response pattern compared to the other groups due to a decreased response rate of their right ear. This finding suggests a group-specific impairment of the speech dominant left hemisphere. In addition, decreased overall response accuracy was observed in male smokers compared to the other experimental groups. Similar adverse effects of smoking were not detected in women. Further, a significant negative correlation was detected between the severity of nicotine dependency and response accuracy in male but not in female smokers. Taken together, these results show that smoking modulates functional brain lateralization significantly and in a sexually dimorphic manner. Given that some psychiatric disorders have been associated with altered brain asymmetries and increased smoking prevalence, nicotinergic effects need to be specifically investigated in this context in future studies.

1. Introduction

The two hemispheres of the human brain are specialized for different cognitive processes, with speech perception and language processing emerging as the most important left hemispheric function (Hugdahl, 2005; Thomsen, Rimol, Ersland, & Hugdahl, 2004). Sex differences in brain lateralization have been widely investigated (e.g., Güntürkün & Hausmann, 2007; McGlone, 1980; Sommer, Aleman, Somers, Boks, & Kahn, 2008; Voyer, 1996). At a functional level, and possibly corresponding to neuroanatomical asymmetries (Chance, Casanova, Switala, & Crow, 2006; Wada, Clarke, & Hamm, 1975, but see Sommer et al., 2008), women generally make use of a more bilateral processing mechanism than men (Güntürkün & Hausmann, 2007; Voyer, 1996). Sex differences have been shown across various tasks of functional brain lateralization, such as dichotic listening (Ikezawa et al., 2008; Meinschaefer, Hausmann, & Güntürkün, 1999; Wadnerkar, Whiteside, & Cowell, 2008) and visual half-field tasks (Güntürkün & Hausmann, 2007; Hausmann & Güntürkün, 1999, 2000). However, not all studies revealed sex differences (Hugdahl, 2003; Sommer et al., 2008), and such controversial findings might at least in part result from the temporary fluctuations of sex hormones during different times in a woman's life, for example, during the menstrual cycle, during pregnancy, and after menopause. These fluctuations are known to elicit dynamic short-term modulation of asymmetric information processing (Bayer, Kessler, Güntürkün, & Hausmann, 2008; Bibawi, Cherry, & Hellige, 1995; Hausmann & Güntürkün, 2000; Hausmann, Becker, Gather, & Güntürkün, 2002; Heister, Landis, Regard, & Schroeder-Heister, 1989; Mead & Hampson, 1996; Rode, Wagner, & Güntürkün, 1995; Sanders & Wenmoth, 1998; Wadnerkar et al., 2008).

In addition to steroid hormones, nicotine consumption has been suggested as another source of variation in functional cerebral asymmetry (Algan, Furedy, Demigoren, Vincent, & Pogun, 1997; Pogun, Demirgören, Pehlivan, & Aydin, 1995), yet its exact role with respect to brain lateralization still remains largely unexplored. This is surprising given that nicotine affects many aspects of cognition, including attention (Hahn, Sharples, Wonnacott, Shoaib, & Stolerman, 2003; Heishman, 1999; Mansvelder, van Aerde, Couey, & Brussaard, 2006; McClernon, Kozink, & Rose, 2008; Mirza & Stolerman, 1998; Stolerman, Mirza, Hahn, & Shoaib, 2000; Wonnacott, Sihpuara, & Balfour, 2005), and there are significant sex differences regarding the central effects of nicotine and smok-

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ing in rodents and human subjects (reviewed in Perkins et al., 2009; Pogun & Yararbas, 2009).Furthermore, nicotine-mediated and sex-specific effects on laterality have been demonstrated in rats (Kanit, Koylu, Erdogan, & Pogun, 2005). Our study therefore specifically examines possible effects of smoking on language lateralization of men and women.

Nicotine, the primary psychoactive component of tobacco smoke, is an agonist in the cholinergic neurotransmitter system with high affinity for the $\alpha 4\beta 2$ nicotinergic receptor subtype widely distributed throughout the central nervous system (Wonnacott et al., 2005). Nicotinergic acetylcholine receptors are abundantly expressed in the prefrontal cortex, which is involved in cognitive processes, such as attention and working memory. Thus, nicotine plays a major role in the neuromodulation of acetylcholine and also interacts with other neurotransmitter systems, such as dopamine (Dani, 2001; Jones, Sudweeks, & Yakel, 1999).

Evidence that nicotine has dramatic impact on attentional processes, particularly in the auditory domain, comes from studies by Jacobsen and colleagues (Jacobsen, Krystal, Mencl, Westerveld, Frost, & Pugh, 2005; Jacobsen, Slotkin, Mencl, Frost, & Pugh, 2007), in which sex-specific effects of nicotine were detected. During auditory attention tasks, men were particularly impaired if they had been exposed to nicotine during either the prenatal or the adolescent phase; however, no attentional impairments were found for males not exposed to tobacco smoke during these critical periods. In contrast, women showed milder, yet still negative impact of nicotine exposure during critical developmental stages. These findings suggest a greater vulnerability of the auditory system elicited by nicotine exposure in men than women. Further support comes from Jacobsen, Picciotto, et al. (2007), who showed that brain activity in the auditory cortex was significantly elevated in adolescents who currently smoked or had been exposed to nicotine during embryonic development. This elevated activation pattern was interpreted to indicate less efficient neural processing.

Given the significant effects of sex-specific modulation of attentional processes by nicotine, the question arises whether nicotine might also modulate functional brain lateralization of speech recognition, requiring attentional resources (Hugdahl, Westerhausen, Alho, Medveden, Laine, & Hämäläinen, 2009; Nicholls & Wood, 1998; Nicholls, Wood, & Hayes, 2001), and thus is apparent at the junction of functional brain lateralization and attention.

The verbal dichotic listening paradigm requires attentional processes (Hugdahl et al., 2009), and offers a reliable measure to assess the extent to which one hemisphere (usually the left) is lateralized for language processing (Hugdahl & Hammer, 1997; Bayazit, Öniz, Hahn, Güntürkün, & Özgören, 2009). The dichotic listening test was first developed by Broadbent (1954) and later linked to hemisphere-specific functions by Kimura (1961). Following the presentation of the dichotic or diotic (homonym) stimuli, subjects report which syllable they perceived. The dichotic listening test reveals a right ear advantage that highly correlates with data from the Wada-test (Hugdahl, Carlsson, Uveberant, & Lundervold, 1997), and it is based on the described coupling of the related ear to the contralateral hemisphere (Ahonniska, Castell, Tolvanen, & Lyytinen, 1993; Kimura, 1961). The use of non-speech stimuli, such as music, emotions, or environmental sounds, elicits a left ear advantage (e.g., Penna et al., 2006). Given this background, the dichotic listening procedure has been widely used to study brain asymmetries (Penna et al., 2006), particularly speech sound processing of the left temporal lobe (Berlin, Lowe-Bell, Cullen, & Thompson, 1973; Hugdahl, 2005; Jäncke, Buchanan, Lutz, & Shah, 2001; Jäncke & Shah, 2002; Penna et al., 2006; Sandmann et al., 2007; Tervaniemi & Hugdahl, 2003). In the current study, we used the dichotic listening task to elucidate whether or not sex-specific effects of nicotine contribute to the modulation of functional brain lateralization.

2. Methods

2.1. Participants

Ninety (48 females, 42 males) healthy, right-handed (EHI: LQ > 50, $M = 90.9$, $SD = 12.2$) participants between 18 and 58 years of age (mean age: 30.68 years, $SD = 10.53$) were recruited from the area of Izmir and Ege University, Turkey. Participants reported no history of any neurological and psychiatric conditions (except for smoking tobacco), and all were native Turkish speakers. The study was approved by the local research ethics committee of the Faculty of Medicine at Ege University, and the study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Informed consent was given by the participants prior to the study. Furthermore, all subjects were screened with audiometric testing (0.750, 1, 1.5, 3, and 6 kHz with MA25, MAICO Diagnostic GmbH) to ensure normal hearing in both ears. None of the subjects had a hearing threshold greater than 20 dB or an interaural difference greater than 10 dB on any frequency.

Based on the individual nicotine dependency score on the Fagerström test (Heatherton, Kozlowski, Frecker, & Fagerström, 1991), the sample comprised 43 smokers and 47 non-smokers, thereby creating six experimental groups – male non-smokers ($n = 20$), male light smokers ($n = 9$), male heavy smokers ($n = 13$), female non-smokers ($n = 27$), female light smokers ($n = 10$), and female heavy smokers ($n = 11$). The Fagerström score, explained in Section 2.3, had to be at least "1" for smokers and "0" for non-smokers. Moreover, smokers reported to consume at least 1 cigarette per day, while non-smokers reported to consume none.There was no significant difference in the distribution of heavy (>10 cigarettes per day) and light ($\leq$10 cigarettes per day) smokers between males and females.

Means and standard deviations regarding age, handedness index (EHI), and nicotine dependency score (FDNT) for each experimental group are provided in Table 1. There were no differences between experimental groups with respect to age and degree of handedness, and female and male smokers did not differ in their nicotine dependency score. 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, Bouma, van Strien, van Schijndel, Barkhof, & Scheltens, 2006; Li, Moore, Tyner, & Hu, 2009;

Table 1
Means and standard deviations of age, EHI (laterality index for handedness), and FNDT (nicotine dependency score) for all experimental groups (female vs. male non-smokers, light smokers, and heavy smokers) for a total of 90 participants.

Group	Non-smokers	Light smokers	Heavy smokers
Males			
Number[a]	$n = 20$	$n = 9$	$n = 13$
Age[a]	$M = 30.55$ ($SD = 10.23$)	$M = 29.67$ ($SD = 11.50$)	$M = 37.00$ ($SD = 10.90$)
EHI[b,c]	$M = 92.25$ ($SD = 13.23$)	$M = 91.11$ ($SD = 10.54$)	$M = 90.77$ ($SD = 9.54$)
FTND[c,d]	$M = 0.00$	$M = 1.89$ ($SD = 1.17$)	$M = 6.00$ ($SD = 1.73$)
Females			
Number	$n = 27$	$n = 10$	$n = 11$
Age	$M = 28.00$ ($SD = 9.58$)	$M = 33.30$ ($SD = 11.61$)	$M = 28.45$ ($SD = 9.76$)
EHI	$M = 92.70$ ($SD = 10.97$)	$M = 93.00$ ($SD = 8.23$)	$M = 82.45$ ($SD = 17.94$)
FTND[d]	$M = 0.00$	$M = 2.20$ ($SD = 1.81$)	$M = 5.18$ ($SD = 1.89$

[a] No differences between groups with respect to age, EHI, and FNDT.
[b] EHI: Edingburgh Handedness Inventory assesses laterality index for handedness.
[c] FTND: Fagerström Test for Nicotine Dependency.
[d] n.a.: not applicable, since all non-smokers had a FTND score = 0.

Obler, Woodward, & Albert, 1984) and because there was a tendency for an interaction ($F(1,39) = 3.28$; $p = 0.078$; $\eta^2 = 0.078$) with male heavy smokers being older than male light smokers and female heavy smokers being younger than female light smokers.

2.2. Handedness and laterality index for dichotic listening

The Edinburgh Handedness Inventory (EHI, Oldfield, 1971) was used to assess handedness by asking the participant for the preferred hand while conducting everyday-life activities, such as writing or throwing a ball. A laterality quotient is obtained by the formula $[(R-L)/(R+L)] \times 100$, resulting in values of $-100 < x < +100$. Only participants with an LQ > 50, indicating right-handedness, were included in the study.

The dichotic laterality index (LI) was calculated for each participant according to the following formula:

$$\text{Laterality Index(LI)} = \frac{(\text{Correct Right Ear Responses} - \text{Correct Left Ear Responses})}{(\text{Correct Right Ear Responses} + \text{Correct Left Ear Responses})} \times 100$$

By definition, the index varies between −100 and +100 and has positive values for right ear advantages, indicating lateralization to the left hemisphere, and negative values for left ear advantages, indicating lateralization to the right hemisphere (Eichele, Nordby, Rimol, & Hugdahl, 2005; Hugdahl, 2005; Penna et al., 2006; Rimol, Eichele, & Hugdahl, 2006).

2.3. Nicotine dependency

The Fagerström Test of Nicotine Dependency (FTND, Heatherton et al., 1991) was employed to assess the degree of nicotine dependency. It consists of 6 multiple choice questions concerning daily habits of tobacco smoking and nicotine craving to yield a score between 0 and 10. High values indicate strong dependency while a value of 0 indicates no dependency.

The FTND, revised from the former Fagerström Tolerance Questionnaire (Fagerström, 1978; Fagerström & Schneider, 1989), has proven to be a valid instrument to assess nicotine dependency, and reliably has been shown to correlate with biochemical markers of tobacco use, such as exhaled CO and cotinine level, (Becona & Garcia, 1995; Fagerström & Schneider, 1989; Heatherton et al., 1991; Pomerleau, Pomerlea, Majchrezak, Kloska, & Malakuti, 1990).

2.4. Procedure

Testing took place individually in a quiet laboratory room. We administered a verbal dichotic listening task using the six classic consonant–vowel syllables: “ba”, “da”, “ga”, “ka”, “pa”, “ta”. Dichotic stimuli pairs, defined as the simultaneous presentation of two non-identical syllables to the right and left ear, were distinguished from diotic stimuli pairs (so called homonyms), consisting of two identical stimuli simultaneously presented to both ears.

Stimuli were digitally recorded natural complex speech sounds produced by an adult Turkish male baritone voice with a mean duration of 350 ms. While forming dichotic syllables, spectral temporal envelopes of the syllables were matched. The differences between the voice onset time of the voiced (“ba”, “da”, “ga”) and voiceless stop consonants (“ka”, “pa”, “ta”) were identified and controlled for voice onset time. All possible combinations of the syllable pairs were applied to both ears. Six homonym pairs and 30 possible combinations of the six consonant–vowel, dichotic syllables were used, which resulted in 36 possible pairs. The inter-stimulus interval was kept constant at 2 s. The stimuli were presented via sound-proof headphones (Beyerdynamic DT 770) at 80 dB. Participants performed 2 practice runs of 12 trials each and 4 test runs of 36 trials each, resulting in a total of 144 test trials for each participant. In order to account for possible differences between right hand and left hand responses, 2 test runs and 1 practice run were answered with the left hand and right hand in a counterbalanced order. Also, in order to minimize possible aural differences between the left and the right headphone channels, headphones were reversed for half of the test runs. 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.

2.5. Statistical analyses

SPSS 12.0 (SPSS Inc., USA) was used for statistical analysis. Responses on the dichotic listening task were subjected to a 2×3 mixed-model repeated measure ANCOVA with SEX (female vs. male) and SMOKING (smoker, light smoker (<10 cigarettes per day), and heavy smokers (≥10 cigarettes per day) as independent factors, EAR (left and right) as the repeated factor, and AGE as covariate. Significant effects were followed up by ANCOVA's posthoc analysis with Bonferroni correction for comparison of differences between individual experimental groups. Partial correlation analyses between performance level (correct responses) and dichotic laterality index were carried out to further explore any potential association on language lateralization and nicotine dependency (Fagerström scores).

3. Results

3.1. Laterality index

The mean (±*SD*) laterality index (LI, as calculated according to the formula above) of all 90 subjects was 40.01 (±27.60), indicating that the verbal dichotic listening task reliably lateralized to the left speech dominant hemisphere. Eighty subjects (88.89%) had a positive LI (45.98 (±22.75)), nine subjects (10.00%; 3 male smokers, 2 females smokers, 4 female non-smokers) had a negative LI (−8.57 (±12.34), and one subject (1.11%; 1 male non-smoker) had a neutral LI of zero. Eliminating those subjects, who had a negative LI, did not alter the results reported here; therefore, analyses include the complete sample.

3.2. Dichotic stimuli analyses

Table 2 provides a summary of means (±*SD*) with respect to Left Ear, Right Ear, Homonym responses, and LI for all experimental groups.

The $2 \times 3 \times 2$ mixed model repeated measure ANCOVA with SEX and SMOKING as between subject variables, LEFT and RIGHT EAR as repeated measure variable, and AGE as covariate revealed a significant Ear effect ($F(1,83) = 16.43$; $p < 0.001$; Cohen's $d = 2.41$; $\eta^2 = 0.17$) with dichotic responses more frequently identified by the right ear ($M = 67.89$ (±19.46)) than by the left ear ($M = 28.09$ (±12.98)), confirming the dominance of the left hemisphere.

Between subject analyses, with average ear responses [(LE + RE/2)] as index of correct stimuli recognition, elicited a main effect of sex ($F(1,83) = 10.87$; $p = 0.001$; Cohen's $d = 0.54$; $\eta^2 = 0.12$) with men exhibiting a lower score ($M = 46.01$ (±6.86))

Table 2
Means and standard deviations of each experimental group for Homonyms, Left Ear responses, Right Ear responses, and Laterality Index.

Group	Non-smokers	Light smokers	Heavy smokers
Males			
HOM	$M = 22.00$ ($SD = 2.81$)	$M = 19.22$ ($SD = 2.95$)	$M = 16.00$ ($SD = 4.53$)
LE	$M = 22.10$ ($SD = 11.83$)	$M = 27.89$ ($SD = 5.71$)	$M = 30.85$ ($SD = 9.32$)
RE	$M = 78.40$ ($SD = 16.17$)	$M = 64.79$ ($SD = 9.96$)	$M = 47.69$ ($SD = 9.24$)
LI	$M = 55.49$ ($SD = 23.75$)	$M = 39.34$ ($SD = 14.41$)	$M = 21.81$ ($SD = 18.54$)
Females			
HOM	$M = 21.85$ ($SD = 3.27$)	$M = 21.70$ ($SD = 2.50$)	$M = 22.82$ ($SD = 1.89$)
LE	$M = 31.30$ ($SD = 15.25$)	$M = 28.20$ ($SD = 13.09$)	$M = 27.91$ ($SD = 15.33$)
RE	$M = 66.59$ ($SD = 21.66$)	$M = 69.40$ ($SD = 16.32$)	$M = 77.00$ ($SD = 19.37$)
LI	$M = 34.33$ ($SD = 31.35$)	$M = 41.84$ ($SD = 26.24$)	$M = 46.21$ ($SD = 30.20$)

HOM: Homonym diotic stimuli when the same syllable was presented on both ear channels.
LE: Left Ear responses are dichotic stimuli correctly identified on the left ear channel.
RE: Right Ear responses are dichotic stimuli correctly identified on the right ear channel.
LI: Laterality Index calculated for dichotic stimuli correctly identified on either ear.

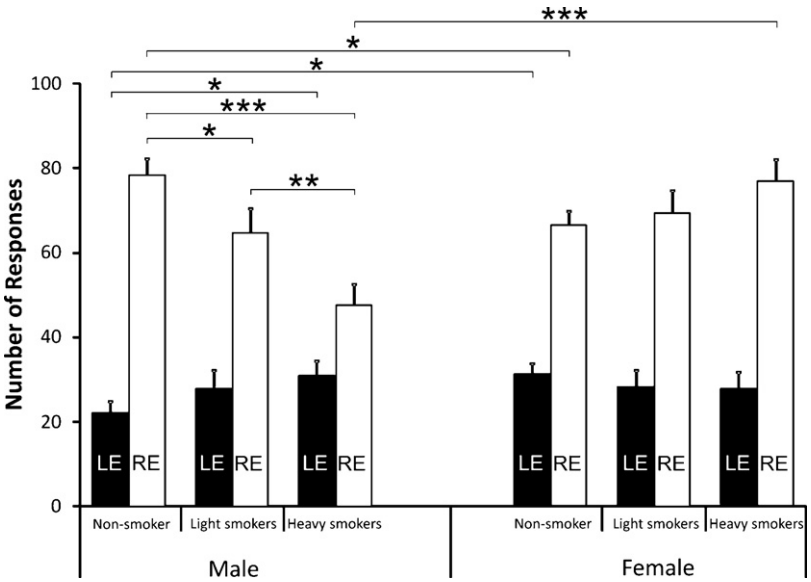

Fig. 1. Separate responses for left ear (LE) and right ear (RE) in male and female non-smoking, light smoking, and heavy smoking participants (*$p < 0.05$; **$p < 0.001$; ***$p < 0.001$). Overall, RE responses were significantly higher than LE responses ($p < 0.001$). Significant differences are indicated between groups for LE and RE comparisons. Among males, smoking quantity was associated with decreased RE and increased LE responses. Among non-smokers, males had increased RE and decreased LE responses compared to females, and RE responses were decreased in heavy smoking males compared to their female peers.

than women ($M = 49.72$ (± 6.77)), and a significant interaction of sex and smoking ($F(2,83) = 10.52$; $p < 0.001$, $\eta^2 = 0.20$). Post hoc comparisons elicited this effect for males ($F(2,38) = 12.76$, $p < 0.001$, $\eta^2 = 0.40$) but not for females. Non-smoking males ($M = 50.25$ (± 5.35)) had higher response scores than light smoking males ($M = 46.33$ (± 3.72), $F(1,26) = 4.52$, $p = 0.043$, Cohen's $d = 0.85$, $\eta^2 = 0.15$), and they also had higher response scores than heavy smoking males ($M = 39.27$ (± 5.22), $F(1,26) = 27.30 < 0.001$, Cohen's $d = 2.08$, $\eta^2 = 0.48$). Light smoking males had higher scores than heavy smoking men ($F(1,26) = 9.32$, $p = 0.007$, Cohen's $d = 1.56$, $\eta^2 = 0.33$). No such differences occurred in the female groups. Further, heavy smoking men ($M = 39.27$ (± 5.22) had significant lower response scores than heavy smoking women ($M = 52.45$ (± 5.76), $F(1,21) = 26.33$, $p < 0.001$, Cohen's $d = 2.40$, $\eta^2 = 0.56$). No other sex differences were found.

There was no within-subject interaction between either Ear * Sex effect or Ear * Smoking. However, the three-way interaction of Ear * Sex * Smoking was significant ($F(1,83) = 7.03$; $p = 0.002$; $\eta^2 = 0.15$). Although smoking did not show any effect in women, the relative contribution of men's left and right ear responses was strongly influenced by the absence versus presence of smoking (Ear * Smoking: $F(1,38) = 12.76$; $p < 0.001$; $\eta^2 = 0.40$) and its quantity, see Fig. 1. In male subjects, left ear responses increased with smoking quantity ($F(2,38) = 3.60$; $p = 0.037$; $\eta^2 = 0.16$). Responses of heavy smoking males were significantly increased ($M = 30.85$ (± 9.32)) compared to non-smoking males ($M = 22.10$ (± 11.83), $F(1,30) = 5.93$; $p = 0.021$; Cohen's $d =$; $\eta^2 = 0.82$). In contrast, right ear responses decreased with increasing smoking quantity ($F(2,38) = 18.84$; $p < 0.001$; $\eta^2 = 0.50$). Non-smoking male subjects ($M = 78.40$ (± 16.17)) had more right ear responses than light smoking males ($M = 64.78$ (± 9.96), $F(1,26) = 5.28$; $p = 0.03$; Cohen's $d = 1.01$; $\eta^2 = 0.17$) and also compared to heavy smokers ($M = 47.69$ (± 9.24), $F(1,30) = 32.23$; $p < 0.001$; Cohen's $d = 2.33$; $\eta^2 = 0.52$). A significant difference also occurred between light and heavy smoking males ($F(1,19) = 13.89$; $p = 0.001$; Cohen's $d = 1.78$; $\eta^2 = 0.42$). No such effects occurred in female participants.

Among the non-smoking groups, we detected increased left ear responses in females ($M = 31.30$ (± 15.25)) compared to males ($M = 22.10$ (± 11.93), $F(1,44) = 4.55$; $p = 0.038$; Cohen's $d = 0.67$; $\eta^2 = 0.09$) and an opposite effect for right ear responses, which was increased in males ($M = 78.40$ (± 16.17)) compared to females ($M = 66.59$ (± 21.66), $F(1,44) = 5.37$; $p = 0.025$; Cohen's $d = 0.62$; $\eta^2 = 0.11$). Among the smoking groups, no sex differences occurred with respect to left ear responses. However, right ear responses were increased in heavy smoking females ($M = 77.00$ (± 19.37) compared to heavy smoking males ($M = 47.69$ (± 9.241, $F(1,21) = 18.80$; $p < 0.001$; Cohen's $d = 1.93$; $\eta^2 = 0.47$).

Indeed, this implication was further supported by a 2×3 (Sex $\times$ Smoking) between subject ANCOVA with Laterality Index (LI) as the dependent variable and Age as covariate. No main effects of Sex and Smoking were found. However, the 2-way interaction of Sex * Smoking was significant ($F(1,83) = 6.11$; $p = 0.003$; $\eta^2 = 0.13$), see Fig. 2. Post-hoc comparisons revealed that this effect was driven by smoking and its quantity of males, i.e., non-smokers ($M = 55.49$ (± 23.75), light smokers ($M = 39.34$ (± 14.41), and heavy smokers ($M = 21.81$ (± 18.54), $F(2,38) = 10.50$; $p < 0.001$; $\eta^2 = 0.36$). Significant differences occurred between non-smoking and heavy smoking males ($F(1,30) = 18.01$; $p < 0.001$; Cohen's $d = 1.58$; $\eta^2 = 0.38$) and between light smoking and heavy smoking males ($F(1,19) = 4.98$; $p = 0.038$; Cohen's $d = 1.06$; $\eta^2 = 0.21$). Among non-smokers, sex difference occurred between males and females ($F(1,44) = 6.52$; $p = 0.014$; Cohen's $d = 0.76$; $\eta^2 = 0.13$), indicating a less lateralized processing in women than men if they do not smoke. Among heavy smoking groups, women ($M = 46.21$ (± 30.20) had a higher LI than their male peers ($F(1,21) = 5.03$; $p = 0.036$; Cohen's $d = 0.97$; $\eta^2 = 0.19$) indicating a more lateralized processing in smoking women compared to smoking men. There were no other sex differences between groups.

3.3. Homonym stimuli analysis

Result patterns similar to laterality analyses were obtained when correct detection of Homonym stimuli (see Table 2) presented on both ear channels simultaneously were analyzed by conducting a 2 (sex) $\times$ 3 (smoking quantity) ANCOVA with age as covariate (Sex: $F(1,83) = 16.84$; $p < 0.001$; Cohen's $d = 0.69$; $\eta^2 = 0.17$; Smoking: $F(2,83) = 4.25$; $p = 0.017$; $\eta^2 = 0.09$; Sex * Smoking: $F(1,83) = 9.00$; $p < 0.001$; $\eta^2 = 0.18$; see Fig. 3). Again, it was the male group whose smoking quantity elicited these effects ($F(2,38) = 9.93$; $p < 0.001$; $\eta^2 = 0.34$), and not the female

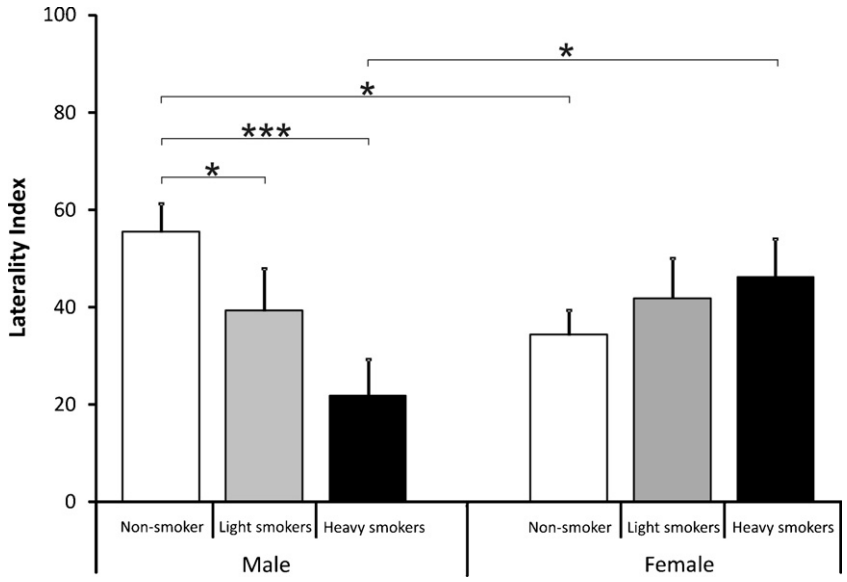

Fig. 2. Laterality index of males and females, subdivided into non-smokers (white), light smokers (grey), and heavy-smokers (black) for the dichotic listening task ($^{*}p < 0.05$; $^{***}p < 0.001$). Heavy smoking males had a lower laterality index than light smoking males and than non-smoking men. Among non-smokers, females had a lower laterality index than males, and among heavy smokers, women had a higher laterality index than men.

group. Significant differences occurred between non-smoking men ($M = 17.32$ (± 4.20)) and heavy smoking ones ($M = 16.00$ (± 4.53), $F(1,30) = 17.09$; $p < 0.001$; Cohen's $d = 1.59$; $\eta^2 = 0.36$) and between the three female groups, i.e. non-smokers ($M = 21.85$ (± 3.27), $F(1,37) = 13.11$; $p = 0.001$; Cohen's $d = 1.48$; $\eta^2 = 0.28$), light smokers ($M = 21.70$ (± 2.50), $F(1,20) = 11.54$; $p = 0.03$; Cohen's $d = 1.56$; $\eta^2 = 0.37$), and heavy smokers ($M = 22.82$ (± 1.89), $F(1,21) = 17.63$; $p < 0.001$; Cohen's $d = 1.97$; $\eta^2 = 0.46$).

3.4. Correlational analyses

Partial correlation analyses between "percentage of correct responses" and "degree of laterality", controlling for age, revealed a significant relationship ($n = 90$; $r = 0.424$; $r^2 = 0.18$; $p < 0.001$) in that stronger laterality was generally associated with more correct responses, thus better performance on the dichotic listening task. This indicates that approximately 18% of the variance of correct responses could be explained by the degree of laterality.

In smokers, a negative correlation occurred between the Fagerström score of nicotine dependency and correct responses in males, again controlling for age ($n = 22$; $r = -0.46$; $r^2 = 0.21$; $p = 0.038$), see Fig. 4, but was non-existent in females ($n = 21$; $r = 0.07$; n.s.). This implies that with increasing severity of nicotine dependency the percentage of correct responses decreased in men, but this was not the case in women.

4. Discussion

The current study addressed accumulating evidence that nicotine, the major psychoactive and addictive component of tobacco,

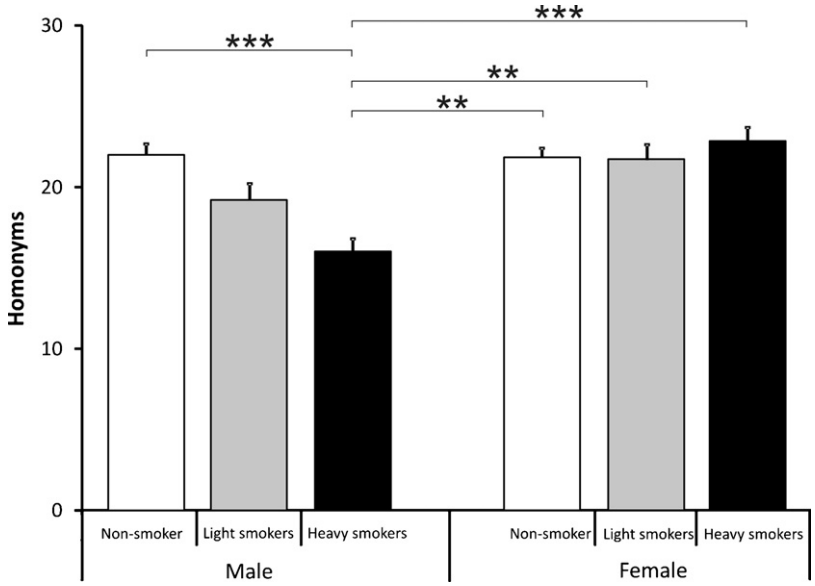

Fig. 3. Homonym responses (simultaneously presented on both ears) of males and females, subdivided into non-smokers (white), light smokers (grey), and heavy smokers (bock) for the dichotic listening task ($^{**}p < 0.01$; $^{***}p < 0.001$). Heavy smoking men had lower scores than non-smoking men and heavy smoking, light smoking and non-smoking females.

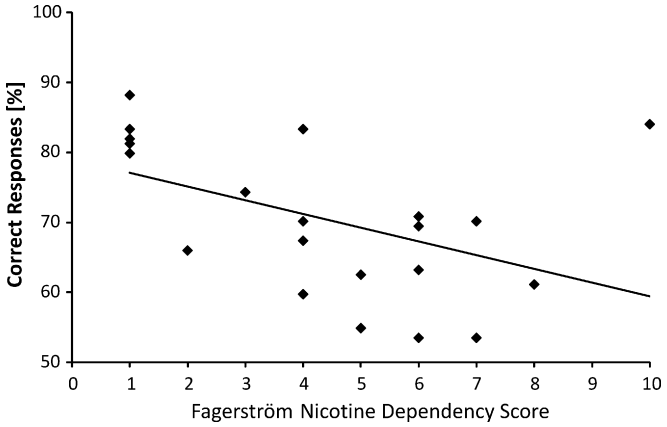

Fig. 4. Scatter plot showing partial correlation, revealing a negative association ($r = -0.46$; $r^2 = 0.21$; $p = 0.038$) between severity of nicotine dependency measured by the Fagerström questionnaire and percentage of correct responses in male smoking participants ($n = 22$).

may be a critical, yet so far largely unexplored source in modulating laterality of the brain, and specifically investigated sex-specific effects of smoking in auditory language lateralization. To this end, we employed a classic consonant–vowel dichotic listening task in smoking and non-smoking men and women, which reliably elicits a left-hemispheric dominance in language processing (e.g., Berlin et al., 1973; Hugdahl, 2005; Jäncke et al., 2001; Jäncke & Shah, 2002; Penna et al., 2006; Sandmann et al., 2007; Tervaniemi & Hugdahl, 2003).

The present study revealed the following results: First, nicotine-dependent men were particularly impaired in stimulus recognition of the dichotic listening task due to decreases of right ear responses, and this was associated with increased smoking quantity. At the same time, and possibly related, they revealed a significantly reduced laterality index, again associated with increased nicotine consumption. Second, a higher laterality index appeared to be generally associated with better recognition performance. Third, a negative association between severity of smoking and laterality index as well as performance was found for men but was non-existent in women. Fourth, within the non-smoking groups, women showed a significantly more bilateral response pattern than men. In contrast, heavily smoking women exhibited a more lateralized processing than heavily smoking men. In conclusion, a more bilateral processing of speech sounds was found in tobacco smoking men, which was associated with prominent impairments of stimulus recognition, particularly due to decreases of right ear responses. No such effects of smoking quantity (either with respect to lateralization or recognition performance) were found in women. This is a remarkable dissociation, suggesting that nicotine may be an important factor that modulates functional brain lateralization.

Our findings that tobacco use adversely affected the performance of males in the dichotic listening task are in accordance with previous results by Jacobsen et al. (2005) and Jacobsen, Slotkin, et al. (2007) where auditory attention was particularly vulnerable in adolescent males who either currently smoked or who had been exposed to nicotine prenatally, or both. In our study, current male smokers were also profoundly impaired in stimulus recognition. These deficits in male smokers were already seen at a level of non-conflict recognition performance for homonym stimuli as well as for dichotically presented stimuli. Our study carefully controlled for comparable hearing thresholds and interaural differences; therefore, general hearing impairments did not account for this effect. A recent paper by Sarter, Hasselmo, Bruno and Givens (2005) suggested that cortical cholinergic hypoactivity may impair the detection process but not alter the primary representation of sensory input. This could explain our findings of men being adversely affected by nicotine in their stimulus detection but not their general hearing thresholds.

The current study also showed, for the first time, that functional brain lateralization of language processing is adversely affected by smoking in males particularly due to decreases of the right (dominant) ear. A change in laterality index can either be caused by the dominant ear to show decreased responses and/or by the non-dominant ear to show increased responses. Although male smokers showed some increase of left (non-dominant) ear responses, they also elicited a dramatic decrease of their right (dominant) ear responses. The adverse effects of nicotine on auditory language lateralization find further support by the observed negative association between severity of nicotine dependence and recognition performance in tobacco smoking males as well as by our finding that better performance was associated with a higher degree of lateralization. These results suggest both a greater general vulnerability of the auditory system and of auditory brain lateralization in particular elicited by nicotine exposure in men. Again, these results support previous studies in which the dichotic listening task generally elicited a left-hemisphere advantage in all groups (e.g., Berlin et al., 1973; Hugdahl, 2005; Jäncke & Shah, 2002; Jäncke et al., 2001; Penna et al., 2006; Sandmann et al., 2007; Tervaniemi & Hugdahl, 2003). Our findings are also in accordance with the Jacobsen et al. (2005), Jacobsen, Slotkin, et al. (2007) studies where nicotine dependent men were more severely impaired in auditory attention than women.

In contrast to men, we found that women were not impaired by smoking. Smoking neither affected general recognition performance nor lateralization in the auditory language processing of women. Our finding, that the laterality index in female smokers was unaffected by the quantity of the cigarettes smoked while it was related to the quantity of tobacco use in male smokers, lends support to previously reported findings that nicotine dose of cigarettes is less important regarding the subjective and, under some conditions, reinforcing effects of smoking in women than in men (Perkins, Jacobs, Sanders, & Caggiula, 2002) and that men benefit from nicotine replacement therapy more than women (reviewed by Perkins, 2001). The result that the auditory attentional performance of women appears to be less vulnerable to nicotine exposure confirms previous results by Jacobsen et al. (2005), Jacobsen, Slotkin, et al. (2007). It remains to be examined whether functional brain lateralization might be more affected in the visual modality in smoking women as has been suggested by the authors (Jacobsen, Slotkin, et al., 2007).

Although widely studied in many domains, sex differences have been largely neglected in addiction research until recently (Wetherington, 2007). However, sex differences are ubiquitously evident in the structural and functional organization of the brain and are reflected in group differences in many cognitive abilities and behaviours. In her reviews, Pogun (2001), Pogun and Yararbas (2009) emphasized sex differences in various aspects of nicotine dependency between males and females, e.g., pharmacokinetics, drug metabolism, addiction and quitting behaviour. Our study found nicotine-modulated sex-specific differences on the performance of the dichotic listening task. Interestingly, when only the non-smoking groups were considered, we observed the traditionally found sex difference with women processing information more bilaterally than men (Hausmann & Güntürkün, 1999, 2000; Ikezawa et al., 2008; Wadnerkar et al., 2008; Meinschaefer et al., 1999). However, it should be noted that other studies did not reveal sex differences (e.g., Sommer et al., 2008; Hugdahl, 2003). In light of these contrasting findings, previously conducted studies attempting to detect sex differences in laterality tasks may need to be reconsidered, querying whether or not smoking status, nicotine dependency and quantity were taken into account. Perhaps some

controversies around sex differences in functional brain lateralization may, at least in part, be reconciled by controlling for tobacco use.

Apart from differences due to sex, previous studies have investigated associations between personality traits and smoking, primarily based on Eysenck's diathese-stress model. In a recent meta-analysis, Munafö, Zetteler and Clark (2007) reported on 25 studies and indicated that on average, extraversion and neuroticism were associated with an elevated likelihood of being a smoker compared to being a non-smoker, in both cases with small overall effect sizes of $d = 0.12$ and 0.19 for neuroticism and extraversion respectively. Studies distinguishing smokers from users of smokeless tobacco products, which do not contain the many additional components of cigarettes, revealed largely similar effects (e.g., Spielberger, Foreyt, Reheiser, & Poston, 1998; Spielberger, Reheiser, Foreyt, Poston, & Volding 2004). When comparing the effect sizes found for the association between these personality traits and tobacco use, with our effect sizes revealed between laterality index and smoking ($ds > 1$), it can be concluded that the association detected between smoking and laterality index cannot be entirely (if at all) due to these personality traits, although we are aware of the notion that personality traits – and likely many other variables – may be associated with tobacco use.

Our study selected smokers and non-smokers based on the Fagerström questionnaire (Heatherton et al., 1991) with the primary goal to correctly categorize tobacco-dependent smokers from non-smokers. We further used one of the FTND questions and detected an effect of smoking quantity on laterality index in male but not in female smokers, suggesting that quantity of nicotine intake, rather than the dependency score per se, will likely provide a more direct link to understanding underlying mechanisms of functional brain lateralization.

We also employed current smokers and non-smokers independent of their previous experience with nicotine, e.g., duration of dependency and number of cigarettes smoked immediately before testing. This bears the advantage of investigating nicotine consumption without acute withdrawal symptoms, which could otherwise lead to disruption of attention and confound with cognitive function (Jacobsen et al., 2005). Furthermore, there are significant individual differences in tobacco addiction and smoking patterns (Perkins, 1995; Pomerleau, 1995; Pomerleau, Collins, Shiffman, & Pomerleau, 1993; Shiffman, 1989; Shiffman & Paton, 1999), precluding the categorization of smokers based solely on their consumption patterns.

However, since our study did not control for smoking history, we cannot conclude whether these effects are due to long-term changes of the brain or short-term effects. Acute, chronic, and prior chronic nicotine exposure all enhance conditioned reinforcement (Brunzell, Chang, & Schneider, 2006; Olausson, Jentsch, & Taylor, 2003; 2004a, 2004b), most likely through the sensitization of the dopamine system (Robbins & Everitt, 2002; Robinson & Berridge, 1993; Taylor & Robbins, 1984) which requires the activation of nicotinergic acetylcholine receptors (nAChRs, Picciotto, Addy, Mineur, & Brunzell, 2008). Some of the clinical effects of smoking are likely to be mediated by dopamine, as there is extensive evidence showing that nicotine/smoking activates brain dopaminergic mesolimbic pathway and increases dopamine release and turnover (reviewed in Sharma & Brody, 2009). While dopamine has received major emphasis, there is also a complex interplay of glutamate, GABA, noradrenalin and serotonin systems in nicotine addiction (reviewed in Barik & Wonnacott, 2009). Chronic nicotine exposure produces a dynamic equilibrium between activation and desensitization of nAChRs. Nicotine-mediated neurotransmitter release can occur after both acute and chronic nicotine exposure even though the prior most likely activates nAChRs and the latter desensitizes them (Benwell & Balfour, 1992; Iyaniwura, Wright & Balfour, 2001). Although the underlying mechanism is still debated (Barik & Wonnacott, 2009), data from both human smokers and animal models demonstrate that nicotine exposure leads to nAChR up-regulation (reviewed in Picciotto et al., 2008) which persists for at least 7 days of smoking abstinence (Staley et al., 2006). Subsequently, although the current study did not control for the participants' lifetime history of smoking, the effect of smoking status on neurotransmitter systems implicated in the dichotic listening task was similar in the subjects.

4.1. Possible neurobiological mechanisms

Nicotine exposure during pregnancy produces deficits in neuron number accompanied by various pathological alterations of neuronal morphology in the neonatal brain (Roy, Seidler, & Slotkin, 2002). These alterations are more prominent when smoking continues into adolescence or beyond, damaging white matter areas and ascending corticofugal fibers, especially of the auditory system (Jacobsen, Picciotto, et al., 2007). Most importantly, the microstructural integrity of the corpus callosum is also affected by heavy and chronic cigarette smoking in adult subjects (Paul et al., 2008), thereby affecting the system that transfers syllabic information during dichotic listening tasks (Bayazit et al., 2009). These structural damages are more pronounced in males and only become equal between sexes when prenatal and adolescent exposure of nicotine is combined (Slotkin et al., 2007). Consequently, males are more vulnerable at already lower levels of nicotine consumption. At the receptor level, early nicotine exposure pathologically alters nicotinic acetylcholine receptors (nAChRs) that are expressed on corticothalamic neurons and that are assumed to mediate top-down control on sensory thalamic relays (King et al., 2003). Nicotine exposure during early postnatal development also results in impaired function of nicotinic acetylcholine receptors (nAChRs) localized on neurons that regulate thalamocortical, and thus bottom-up auditory input (Liang et al., 2006). These changes of transmission between thalamic and cortical structures are possibly one of the key factors that could mediate the results of the current study, as outlined below.

Binding of nicotine to nAChRs increases permeability to both Na^+ and Ca^+ and exerts predominantly modulatory effects on cellular excitability (Wonnacott et al., 2005). Nicotinic AChRs are also abundant within axons of ascending myelinated auditory thalamocortical fibers and their activation results in increased axonal excitability (Kawai, Lazar, & Metherate, 2007). As a result, nicotine is able to lower 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, Pereira, Eisenberg, & Albuquerque, 2000; Rudnick, Koehler, Picciotto, & Siegel, 2009; Sarter et al., 2005). However, this augmenting effect disappears, when chronic nicotine exposure had pathologically altered auditory microcircuitry during neonatal developmental time periods (Liang et al., 2006).

These nicotine-induced changes of synaptic transmission importantly affect attention-demanding tasks, since activation of cholinergic receptors enhance cortical processing of thalamic input and suppress retrieval of internal associations, thereby further promoting sensory input processing (Ernst et al., 2001; Hahn et al., 2003; Sarter, Givens, & Bruno, 2001, 2005). Recent dichotic listening studies show that during task execution attentional control is biased towards the right ear (Hugdahl et al., 2009). The same is found for lateralized word processing in the visual modality (Nicholls et al., 2001). Hugdahl et al. (2009) suggest that a part of the right-ear-advantage results from this bottom-up attentional

bias, while top-down attentional processes are required to process speech in the left ear/right-hemisphere. This implies that nicotine can affect dichotic listening performance by altering nAChRs in the bottom-up thalamocortical auditory pathway (Sarter et al., 2005). However, from what was said above, mild nicotine consumption should promote a right-ear-advantage by increasing attention-mediated synaptic enhancement of the excitability of thalamocortical auditory fibers in the left hemisphere. Why then did we see a sex-specific decrease of asymmetry, especially in heavy smoking males?

Nicotine is a neuroteratogen that disrupts neuronal functions during developmental periods and beyond in a sex-specific way (Slotkin et al., 2007). This differential effect on male and female brains is not special to nicotine but extents to substances and events that injure the brain (Vagnerova, Koehler, & Hurn, 2008). Even male neurons in cell cultures are more susceptible to diverse pharmacological insults than female cells (Du et al., 2004). In the intact brain, progesterone reduces the expression of proinflammatory 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) that positively affect functional recovery (Marques-Vidal et al., 1995). Thus, especially heavy smoking males risk neural damage to auditory thalamocortical transmission and its attentional gating mechanisms. We believe this to be the reason why we observed that in our smoking male subjects right ear responses were selectively impaired while left ear responses increased. This selective impairment of the right ear/left hemisphere cannot be explained by a general hearing deficit, which would have affected both ears. Instead, it is probably due to the sex- and nicotine-dependent reduction of the privileged right ear attentional bias in the intact brain that is typical for hearing of language sounds (Best & Avery, 1999). Although recognition of homonym responses was also slightly reduced in the male smoking group, this may have resulted also from a right ear detection deficit projecting into the language dominant left hemisphere. For instance, to the extent that nicotine might impair bottom-up attentional processing by acting on the cholinoceptive thalamocortical nerve fibers of the auditory system (Kawai et al., 2007; Jacobsen, Picciotto, et al., 2007), the male nicotine-dependent brain might be particularly vulnerable to correctly recognize speech sounds with its right ear/left hemisphere.

Taken together, our neurobiological model departs from the observation that smoking, especially when starting early and consuming great quantities over extended periods of time, cause structural impairments at many levels of the brain. Relevant for dichotic listening are especially the axonal damages in the ascending thalamocortical fibers that transfer auditory input of syllabic information. Since dichotic listening involves language material and thus activates a default attentional bias towards right ear input, structural impairments of attention mediating mechanisms in the thalamocortical system will reduce right ear superiority, thereby increasing the likelihood of recognition of left ear input. Together, this will result in a reduction of the laterality index. If structural damage is less severe or even absent, smoking could in principle even increase right ear advantage, since the nicotinic enhancement of transmission along the auditory thalamocortical fibers would further promote the attentional bias towards the right ear in dichotic listening experiments. Although speculative at the present point, the slight but not significant increase of the laterality index in smoking women could have resulted from their sex-specific neuroprotective condition (resulting in minor or no structural damage) that is nevertheless open to smoking-induced enhancements of nAChRs within auditory thalamocortical axons (producing further gating of left hemisphere language input).

4.2. Summary and outlook

Our results show that smoking modulates functional brain lateralization significantly and in a sexually dimorphic manner by reducing right ear recognition rate in males, thereby reducing their laterality bias. This raises important questions for further research, possibly elucidating neuropsychological and neural mechanisms underlying psychiatric disorders. Some psychiatric disorders have been associated with deviating brain lateralization for a number of decades, for instance, schizophrenia (Crow, 1997; Mitchell & Crow, 2005; Sommer, Aleman, Ramsey, Bourma, & Kahn, 2001) and attentional hyperactivity disorder (ADHD, Hale et al., 2005; Hale, Zaidel, McGough, Phillips, McCracken, 2006). At the same time, both schizophrenia (Kumari & Postma, 2005) and ADHD (Gray & Upadhyaya, 2009) are marked with a significantly elevated proportion of nicotine-dependent patients compared to the average population. The idea that laterality deviations seen in these patients might in fact be due, at least in part, to secondary artefacts of smoking rather than of the disease itself (Herzig, Tracy, Munafö, & Mohr, 2010), calls for the need to conduct further research. None of the studies relating brain laterality to psychiatric diseases, such as schizophrenia or ADHD, have so far considered the unequal proportion of nicotine consumption and severity of dependence between patients and healthy subjects. Ultimately, by controlling for and nicotine use in future studies, we might be able to gain important insights into possible underlying neuropsychological and neurobiological mechanisms of functional brain lateralization and cognitive behaviour in general.

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