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FOXP2 variation modulates functional hemispheric asymmetries for speech perception

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ABSTRACT

Left-hemispheric language dominance is a well-known characteristic of the human language system, but the molecular mechanisms underlying this crucial feature of vocal communication are still far from being understood. The forkhead box P2 gene *FOXP2*, which has been related to speech development, constitutes an interesting candidate gene in this regard. Therefore, the present study was aimed at investigating effects of variation in *FOXP2* on individual language dominance. To this end, we used a dichotic listening and a visual half-field task in a sample of 456 healthy adults. The *FOXP2* SNPs rs2396753 and rs12533005 were found to be significantly associated with the distribution of correct answers on the dichotic listening task. These results show that variation in *FOXP2* may contribute to the inter-individual variability in hemispheric asymmetries for speech perception.

1. Introduction

One of the most remarkable aspects of vertebrate brain organization is the presence of structural and functional asymmetries between the hemispheres (Manns & Güntürkün, 2009; Ocklenburg & Güntürkün, 2012; Tervaniemi & Hugdahl, 2003; Vallortigara & Rogers, 2005; Westerhausen et al., 2006). In the human brain, certain cognitive and motor functions such as language and handedness show particularly pronounced asymmetry. In the majority of the population, both production and perception of language are largely mediated by left-hemispheric fronto-temporal networks (e.g., Buchanan et al., 2000; Friederici, 2011; Hauk & Pulvermüller, 2011; Hugdahl, 2011; Van der Haegen, Cai, Seurinck, & Brysbaert, 2011; also see Mitchell & Crow, 2005 for a review of right hemisphere language functions). Even though more than 130 years ago the specialization of the left hemisphere for language was one of the earliest observations of brain asymmetry (Broca, 1861), the molecular mechanisms underlying the development of this and other hemispheric specializations and their behavioral and physiological implications remain largely unknown. Apart from multiple factors such as developmental events, neurochemical asymmetries, experience and disease, genetic models have also been proposed to account for cerebral asymmetry (Annett, 2002; Geschwind, Miller, DeCarli, & Carmelli, 2002; McManus, 2002; Toga & Thompson, 2003). However, although there are a number of candidates, no gene or pathway has yet been clearly identified as a determinant of lateralization (e.g., Ocklenburg et al., 2011; Ocklenburg et al., 2013; Scerri et al., 2011; Sun & Walsh, 2006; Van Agtmael, Forrest, Del-Favero, Van Broeckhoven, & Williamson, 2003). One of these candidates for language lateralization is the *forkhead box P2* gene, *FOXP2*, a developmental transcriptional regulator which controls the growth and differentiation of a class of neurons destined to innervate tissues primarily involved in speech production (Vernes et al., 2006). Mutations in *FOXP2* cause severe developmental verbal dyspraxia, a disorder that leads to an inability to conduct the appropriate orofacial movements to generate speech (Fisher, Vargha-Khadem, Watkins, Monaco, & Pembrey, 1998; Hurst, Baraitser, Auger, Graham, & Norell, 1990; Kang & Drayna, 2011). Additionally, *FOXP2* polymorphisms have been linked to neuropsychiatric and developmental disorders like schizophrenia, autism spectrum disorders or dyslexia which have all been shown to be related to reduced language lateralization (Li et al., 2013; Sanjuán et al., 2006; Španiel et al., 2011 but see: Bleich-Cohen et al., 2012; Gong et al., 2004; Hugdahl et al., 2007; Iliadou, Kaprinis, Kandylis, & Kaprinis, 2010; Kleinhans, Müller, Cohen, & Courchesne, 2008; Sanjuan et al., 2005; Sommer, Ramsey, Kahn, Aleman, & Bouma, 2001; Wilcke et al., 2012). Interestingly, the possible link between *FOXP2* and language lateralization is not limited to patient cohorts, since *FOXP2* variation has been shown to

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correlate with language-related brain activity of healthy adults (Pinel et al., 2012). Specifically, Pinel et al. (2012) showed that variation in two *FOXP2* SNPs (rs6980093 and rs7799109) was related to interindividual variability of activation in the left inferior frontal cortex during a reading task.

Taken together, these lines of evidence suggest that variation in *FOXP2* may contribute to the extent or direction of individual language lateralization. Thus, the aim of the present study was to examine a possible association of *FOXP2* and hemispheric asymmetries for speech perception. We genotyped four *FOXP2* single nucleotide polymorphisms (SNPs) and two microsatellite markers in a sample of 456 healthy German students, and examined their association with two behavioral markers of language lateralization: an auditory dichotic listening task (Green, Hugdahl, & Mitchell, 1994; Hugdahl, 2011; Løberg, Jørgensen, & Hugdahl, 2002; Løberg, Jørgensen, & Hugdahl, 2004) and a visual half-field paradigm (Hausmann & Güntürkün, 2000; Rode, Wagner, & Güntürkün, 1995), both comprising verbal stimuli. We assumed that individuals carrying genotypes previously identified as risk genotypes for disorders linked to reduced language lateralization also exhibit reduced language lateralization in our healthy sample.

2. Material and methods

2.1. Participants

The sample consisted of 456 unrelated adults (mean age: 23.76 years, SD: 2.81; 265 women; 191 men). All participants were of Caucasian descent for at least two generations and had no history of any neurological or psychiatric diseases. Only native German speakers with unimpaired hearing capabilities (as tested using audiometric screening) were included in the sample. On average, participants received 14.61 years of education (SD: 2.43). All participants were tested with a neuropsychological test battery including a verbal intelligence test and measures of fluid intelligence and executive functioning (Arbuthnott & Frank, 2000). Moreover, participants were screened for depression using the BDI (Beck Depression Inventory; Beck & Alford, 2008) and anxiety using the ASI (Anxiety Sensitivity Index; Taylor & Cox, 1998). As analyzed in ANOVAs, *FOXP2* genotype groups did not significantly differ in any of the neuropsychological or psychiatric measures (all $p > 0.15$). All participants gave written informed consent and were treated in accordance with the declaration of Helsinki. The study was approved by the ethics committee of the Medical Faculty at the Ruhr-University Bochum, Germany.

2.2. Genotyping

For non-invasive sampling, exfoliated cells were brushed from the oral mucosa of the participants. Three different samples were retrieved from every participant, one at the beginning of the test session, the second after 1.5 h, and the third at the end of the test session. Samples were immediately refrigerated after being taken, and were kept refrigerated until further use. DNA isolation was performed with QIAamp DNA mini Kit (Qiagen GmbH, Hilden, Germany). Overall, four *FOXP2* SNPs (rs2396722, rs12533005, rs2396753 and rs17137124) and two microsatellite markers (MS1 and MS2) were genotyped. All four SNPs are intronic, and have previously been associated with cognitive pathology (Sanjuán et al., 2006; Tolosa et al., 2010; Wilcke et al., 2012; Zhao et al. 2010; Španiel et al., 2011). Genotyping of the four *FOXP2* SNPs was conducted by polymerase chain reaction (PCR) and differential enzymatic analysis with the PCR restriction fragment length polymorphism method. Genotyping of the two *FOXP2* microsatellite repeats was performed on the Beckman Coulter CEQ8000 8-capillary system using a fluorescence 5'FAM labeled tailed oligonucleotide added to the 5′-part of the sequence specific primer as described before (Jagiello et al., 2004). PCR amplification of the $(CA)_n$ microsatellite repeat at position chr7:114059757-114059802 (MS1) was performed using 5′-CATCGCTGATTCGCACATTGCCGTCAAAAAACCTCTGTG-3′ and 5′-GCAGGTGGATGCAATGGTAAG-3′ as the forward and reverse primer pairs, respectively. For the $(CA)_n$ microsatellite repeat at position chr7:114221112-114221169 (MS2) the primer pairs 5′-CATCGCTGATTCGCACATCAGCAGTCAAAGGCCAATAGAA-3′ and 5′-ACAGAGCCAGACTGCATCTCAA-3′ were used. All primers were designed with the Primer Express 2.0 Software (Applied Biosystems, Foster City, USA). All other details of the methodology and primer sequences are available upon request.

2.3. Experimental procedure

Since language lateralization has been shown to be correlated with left- or right sided hand- or foot-preferences (e.g., Elias & Bryden, 1998; Hund-Georgiadis, Lex, Friederici, & von Cramon, 2002), handedness and footedness were assessed in order to be able to determine if possible effects were specific for language lateralization or merely secondary effects of an association between genetic variation and individual limb preferences. Handedness was assessed using the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), and footedness using the Waterloo Footedness Questionnaire (WFQ; Elias & Bryden, 1998; Elias, Bryden, & Bulman-Fleming, 1998).

Language lateralization was assessed using an auditory dichotic listening paradigm and a visual half-field paradigm, both of which were programmed using Presentation® software (Neurobehavioral Systems, Inc., Albany, USA). For the dichotic listening task, syllable pairs consisting of two out of six different consonant–vowel (CV) syllables (ba, da, ga, ka, pa, ta) were used as stimuli. Stimuli had a mean duration of 350 ms, and were presented using DT 770 Pro headphones (Beyerdynamic GmbH, Heilbronn, Germany) at 80 dB. After stimulus presentation, participants had to press one of six keys labeled with the six CV pairs on a customized reaction pad to indicate the syllable they had perceived best. The interstimulus interval was two seconds. Participants first performed two practice runs of 12 trials each to get accustomed to the task (practice runs were not included in the analysis), and subsequently completed four test runs of 30 trials each, in which all 30 possible dichotic combinations of the syllable pairs were applied. Thus, the total number of trials was 120. On two of the four test runs participants had to press the reaction keys with the left hand, and on the other two with the right hand, the order of the block being counter-balanced. Furthermore, in order to account for any possible headphone channel effects, the headphones were reversed for two of the four test runs in counter-balanced order.

For the visual half-field paradigm, 60 abstract German nouns (e.g., "Niveau" or "Macht") with a horizontal size of 4° were used as stimuli. Prior to starting the task, participants were asked to place their head on a chin rest located 57 cm away from a standard 17 in. computer monitor, and instructed to focus on the fixation cross in the middle of the screen during the task. Each trial started with the presentation of the fixation cross for 2000 ms. Subsequently, a stimulus was presented centrally for 130 ms, followed by presentation of the fixation cross for 2000 ms. Then, a second stimulus was presented for 130 ms, either 2.2° to the left or the right of the fixation cross. Participants were instructed to indicate as quickly and as accurately as possible whether the two presented stimuli were the same word or not by pressing one of two buttons. On half of the trials, participants had to react with their right hand, and on the other half with their left hand, in counter-balanced order. Overall, there were 120 trials, 60 with identical words and 60 with different words, in pseudo-randomized order.

2.4. Statistical analysis

Genotype frequencies conformed to Hardy–Weinberg equilibrium (all p's > 0.18) as determined using the online version of the program DeFinetti (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). All analyses were conducted assuming a dominant model, so that the rare homozygous and the heterozygous genotypes were combined to one group. In case of MS1 and MS2, the homozygotes of the most common allele were compared with the heterozygotes with the most common allele, and all other rarer genotypes, respectively. For each polymorphism, handedness and footedness LQs were analyzed using independent samples t-tests. Moreover, performance on the dichotic listening task and the visual half-field task was analyzed using a 2 × 2 repeated-measures analyses of variance (ANOVA) with the within-subjects factor side (left ear, right ear) and the between-subjects factor genotype. In order to correct for multiple comparisons, effects were considered significant when the p-value was less than 0.05/6 = 0.0083 (Bonferroni correction).

3. Results

3.1. Handedness and Footedness

Overall, participants had a mean handedness LQ of 70.76 (SD: 51.53), with 48 individuals (10.5%) being left-handed (LQ between −100 and 0) and 408 (89.5%) being right handed (LQ between 0 and 100). For footedness, the average LQ was 43.76 (SD: 42.75), 67 individuals (14.7%) being left- and 389 (85.3%) being right-footed. The results of the handedness and footedness questionnaires are shown in Table 1. Overall, none of the effects reached significance (all $p > 0.05$).

3.3. Dichotic listening task

For the Dichotic Listening Task, the average Li was 40.44 (SD: 32.02) for correct answers and −2.44 (SD: 4.46) for reaction times, both indicating a right ear/left hemisphere dominance on this task. The results of the ANOVAs for the different *FOXP2* polymorphisms are reported in Table 2 (correct answers) and Table 3 (reaction times).

For correct answers, the key interaction genotype by ear reached significance for two SNPs. For rs12533005, this interaction ($F_{(1,448)} = 8.68$; $p = 0.003$; $\eta^2 = 0.02$) indicated that carriers of at least one C allele ($n = 328$) had a more pronounced left hemisphere/right ear dominance (left ear: 29.81, SD = 16.05; right ear: 76.79, SD = 18.79; difference: 46.98) than individuals homozygous for the G allele (left ear: 35.15, SD = 18.02; right ear: 71.24, SD = 20.83; difference: 36.09, $n = 127$). For rs2396753, the interaction ($F_{(1,448)} = 7.46$; $p = 0.007$; $\eta^2 = 0.02$) indicated that carriers of at least one C allele had a more pronounced left hemisphere / right ear dominance (left ear: 29.75, SD = 16.04; right ear: 76.87, SD = 18.85; difference: 47.12, $n = 305$) than individuals homozygous for the A allele (left ear: 34.44, SD = 17.81; right ear: 71.93, SD = 20.46; difference: 37.49, $n = 150$). In addition to the analysis of correct answers, we also investigated whether genetic variation in the different *FOXP2* polymorphisms had a significant impact on false detection rates on the Dichotic Listening Task. The lowest p-value was observed for rs17137124 ($t_{(448)} = 2.39$; $p = 0.02$), but none of the effects reached significance after correction for multiple comparisons. For reaction times, the key interaction genotype by ear failed to reach significance for all polymorphisms (all $p > 0.08$).

To further investigate the observed effects, we used Spearman correlation coefficients to correlate the genotype (coded 0 for 'homozygous for the major allele', 1 for 'heterozygous' and 2 for 'homozygous for the minor allele') with the Li on the Dichotic Listening Task in order to explore possible linear relationships between allele dosage and lateralization. For rs12533005, we observed a significant positive relationship (Spearman correlation coefficient: 0.12, $p = 0.005$), indicating a positive relationship between the number of C alleles and the strength of left-hemispheric language dominance. For rs2396753, the effect only reached nominal significance ($p = 0.02$), while it failed to reach significance for all other polymorphisms (all $p > 0.16$).

Table 1
Results of the handedness and footedness questionnaires (LQs) for the different *FOXP2* polymorphisms.

	Handedness	Footedness
MS1	$p = 0.07$	$p = 0.15$
MS2	$p = 0.83$	$p = 0.27$
rs12533005	$p = 0.81$	$p = 0.37$
rs17137124	$p = 0.37$	$p = 0.06$
rs2396722	$p = 0.78$	$p = 0.93$
rs2396753	$p = 0.12$	$p = 0.68$

Table 2
Results of the dichotic listening task (correct answers) for the different *FOXP2* polymorphisms. For effects significant after Bonferroni correction ($p < 0.0083$), the effect sizes are given as the proportion of variance accounted for (partial η^2).

	Main effect ear	Main effect genotype	Interaction
MS1	$p < 0.001$; $\eta^2 = 0.54$	$p = 0.36$	$p = 0.51$
MS2	$p < 0.001$; $\eta^2 = 0.60$	$p = 0.23$	$p = 0.99$
rs12533005	$p < 0.001$; $\eta^2 = 0.53$	$p = 0.82$	$p = 0.003$; $\eta^2 = 0.02$
rs17137124	$p < 0.001$; $\eta^2 = 0.55$	$p = 0.02$	$p = 0.27$
rs2396722	$p < 0.001$; $\eta^2 = 0.59$	$p = 0.54$	$p = 0.77$
rs2396753	$p < 0.001$; $\eta^2 = 0.56$	$p = 0.76$	$p = 0.007$; $\eta^2 = 0.02$

Table 3
Results of the dichotic listening task (reaction times) for the different *FOXP2* polymorphisms. For effects significant after Bonferroni correction ($p < 0.0083$), the effect sizes are given as the proportion of variance accounted for (partial η^2).

	Main effect ear	Main effect genotype	Interaction
MS1	$p < 0.001$; $\eta^2 = 0.18$	$p = 0.74$	$p = 0.96$
MS2	$p < 0.001$.;$\eta^2 = 0.21$	$p = 0.82$	$p = 0.56$
rs12533005	$p < 0.001$; $\eta^2 = 0.16$	$p = 0.38$	$p = 0.09$
rs17137124	$p < 0.001$; $\eta^2 = 0.18$	$p = 0.66$	$p = 0.67$
rs2396722	$p < 0.001$; $\eta^2 = 0.20$	$p = 0.19$	$p = 0.89$
rs2396753	$p < 0.001$; $\eta^2 = 0.18$	$p = 0.07$	$p = 0.12$

3.3. Visual half-field task

For the visual half-field paradigm, the average Li was 3.14 (SD: 4.86) for correct responses and 0.13 (SD: 3.06) for reaction times. The results of the ANOVAs for the *FOXP2* polymorphisms are reported in Table 4 (correct answers) and Table 5 (reaction times). For both correct answers and reaction times, the key interaction genotype by ear failed to reach significance for all SNPs and MSs (all $p > 0.06$).

3.4. Correlation between limb preferences and language lateralization

Handedness LQ correlated significantly with footedness LQ ($r = 0.63$, $p < 0.001$) as well as with both dichotic listening LIs (correct responses: $r = 0.10$, $p < 0.05$; reaction times: $r = -0.10$, $p < 0.05$). Footedness LQ correlated significantly with dichotic listening reaction times Li ($r = -0.12$, $p < 0.05$).

Table 4
Results of the visual half-field task (correct answers) for the different *FOXP2* polymorphisms. For effects significant after Bonferroni correction ($p < 0.0083$), the effect sizes are given as the proportion of variance accounted for (partial η^2).

	Main effect ear	Main effect genotype	Interaction
MS1	$p < 0.001$; $\eta^2 = 0.27$	$p = 0.82$	$p = 0.37$
MS2	$p < 0.001$.;$\eta^2 = 0.31$	$p = 0.88$	$p = 0.42$
rs12533005	$p < 0.001$; $\eta^2 = 0.27$	$p = 0.35$	$p = 0.50$
rs17137124	$p < 0.001$; $\eta^2 = 0.28$	$p = 0.07$	$p = 0.25$
rs2396722	$p < 0.001$; $\eta^2 = 0.30$	$p = 0.77$	$p = 0.22$
rs2396753	$p < 0.001$; $\eta^2 = 0.29$	$p = 0.26$	$p = 0.35$

Table 5
Results of the visual half-field task (reaction times) for the different *FOXP2* polymorphisms. For effects significant after Bonferroni correction ($p < 0.0083$), the effect sizes are given as the proportion of variance accounted for (partial η^2).

	Main effect ear	Main effect genotype	Interaction
MS1	$p = 0.44$	$p = 0.82$	$p = 0.94$
MS2	$p = 0.35$	$p = 0.25$	$p = 0.38$
rs12533005	$p = 0.59$	$p = 0.31$	$p = 0.38$
rs17137124	$p = 0.54$	$p = 0.15$	$p = 0.46$
rs2396722	$p = 0.22$	$p = 0.83$	$p = 0.42$
rs2396753	$p = 0.43$	$p = 0.51$	$p = 0.59$

4. Discussion

The present study was focused on investigating the relevance of different *FOXP2* polymorphisms for language lateralization. In line with the large body of literature on language lateralization (e.g. Corballis, 2012; Dym, Burns, Freeman, & Lipton, 2011; Hirnstein, 2011; Ocklenburg, Güntürkün, & Beste, 2011; Westerhausen & Hugdahl, 2008), the results from both the dichotic listening and the visual half-field task indicated that - on average – participants showed left hemispheric language dominance. Interestingly, the extent of this asymmetry was modulated by *FOXP2* variation for the auditory dichotic listening task while no such association was found for the visual half-field task.

Two intronic *FOXP2* SNPs in high *linkage disequilibrium* (LD, $r^2 = 0.77$) with each other, rs2396753 and rs12533005, were found to be significantly associated with the distribution of correct answers on the dichotic listening task. With regard to rs2396753, carriers of at least one C allele had a more pronounced left-hemispheric language dominance than individuals homozygous for the A allele. As yet, three studies have linked this SNP to schizophrenia (but see: Jamadar et al., 2011), a psychiatric disorder associated with reduced right-ear advantage in the dichotic listening task (e.g. Hugdahl et al., 2007). Sanjuán et al. (2006) found significant differences in the genotype and allele frequencies between schizophrenic patients with auditory hallucinations and healthy controls, with patients showing a higher frequency of the C allele. An association of this SNP with auditory hallucinations in schizophrenia was further supported by the findings of Tolosa et al. (2010) who found that a *FOXP2* haplotype containing the rs2396753 A allele could be a protective factor for auditory hallucinations. Moreover, Španiel et al. (2011) showed that in schizophrenic patients the rs2396753 C allele is linked to grey matter volume reductions in several brain regions, including both Broca's and Wernicke's area as well as the superolateral and medial temporal cortex in both hemispheres. Based on these findings, however, one would expect carriers of the C allele to show reduced language lateralization in the present study. Since healthy cohort carriers of the C allele instead showed more pronounced language lateralization, the present data may indicate that differential ontogenetic processes occur for language lateralization in schizophrenic and healthy individuals, or that epistatic interactions between *FOXP2* and schizophrenia susceptibility genes may exist.

For the rs12533005 SNP, left-hemispheric speech perception dominance was more pronounced in carriers of at least one rare C allele than in individuals homozygous for the G allele. Rs12533005 has previously been investigated by Ribasés et al. (2012) who found an association between this variation and adulthood ADHD in a German but not in a Spanish cohort. Interestingly, Wilcke et al. (2012) reported a nominal significant association of the rs12533005 GG genotype with dyslexia, a disorder that has previously been linked to reduced language lateralization (Iliadou et al., 2010). Furthermore, these authors investigated the relation between rs12533005 GG genotype and brain activity as measured using fMRI during a phonological processing task, reporting that carriers with the G allele showed reduced activation in the angular and the supramarginal gyrus. Since these brain regions have previously been linked to phonological language processing, Wilcke et al. (2012) argued that these temporo-parietal brain areas may show a functional deficit in carriers of the G allele. Taken together, these findings show that variation in *FOXP2* modulates language lateralization, presumably by affecting temporal and temporo-parietal brain functions. The SNPs that are closely associated are located in non-coding regions where they have no obvious function. Although differential allelic expression of *FOXP2* depending on rs12533005 alleles is suspected (Wilcke et al., 2012), further work is required to determine the functional variations and to finally clarify the underlying biological mechanisms.

Interestingly, the findings by Wilcke et al. (2012) may also explain why we did not observe any effect of *FOXP2* variation on handedness. Handedness and language lateralization are highly correlated, with about 95% of the right-handers and 75% of the left-handers showing left-hemispheric language dominance (Bethmann, Tempelmann, De Bleser, Scheich, & Brechmann, 2007; Flöel, Buyx, Breitenstein, Lohmann, & Knecht, 2005). Due to this high correlation between the two phenotypes, several models of asymmetry development assume that handedness and language lateralization are determined by the same single gene (e.g., Annett, 2002; McManus, 2002). For example, according to the right shift theory developed be Annett (2002), both right handedness and left-hemispheric language dominance are determined by a single gene with two alleles. While the right shift (RS+) allele leads to an increased chance of being right handed and left-dominant for language, the absence of this allele results in a 50:50 chance of being either left- or right-handed. Thus, individuals with two RS + alleles should have the highest probability of being right-handed/left language dominant, while this probability is reduced in heterozygous individuals and lowest in individuals homozygous for the chance allele. While we also observed a correlation between handedness LQ and dichotic listening performance, the association between *FOXP2* variation and lateralization was restricted to dichotic listening performance. Although this finding is in contrast to the theories put forward by Annett (2002) and McManus (2002), it is in accordance with the findings of Wilcke et al. (2012). According to Price (2010), the left angular gyrus is relevant for semantic retrieval, while activation in the supramarginal gyrus increases when incomprehensible sentences are processed. Thus, both brain areas are highly important for language processing but hardly relevant for handedness. If the effect of *FOXP2* on language lateralization does indeed rely on functional changes in these language-related areas, one would not expect an effect on handedness. While further research is needed to explore this idea, our results at least suggest that handedness and language lateralization rely on partly independent genetic backgrounds, and that a better understanding of the ontogenesis of language lateralization can only be achieved if its specific neurobiological background is integrated into theories about its development. Furthermore, the present results argue against a single gene model for language lateralization. For both *FOXP2* SNPs, the variance in dichotic listening performance asym-

metry explained by genetic variation was only 2%. Thus, our findings support the idea that functional language lateralization is a quantitative and multifactorial phenotype, as recently suggested for structural brain asymmetries by Rentería (2012).

One minor methodological issue has to be taken into account when interpreting the results of the present study. While subjects were screened by self-report to eliminate those with known neurologic or psychiatric disorders, they were not asked directly whether or not they had a diagnosis of dyslexia. Future studies investigating the relationship between *FOXP2* and language lateralization should address this issue by including a dyslexia questionnaire.

Notably, variation in *FOXP2* in the present study was associated with performance differences on the auditory dichotic listening but not the visual half-field task. Moreover, while both of these tasks presumably reflect the direction and extent of hemispheric language dominance, we did not find a significant correlation between the accuracy rates or between the reaction times on the two tasks. These findings are in line with the results of a study by (Kim and Levine (1992)) who correlated performance on a verbal dichotic listening task with performance on a visual half-field task with word stimuli and also found no significant correlation between the two ($r = -0.185$, n.s.). The analysis by Kim and Levine (1992) further revealed that there seem to be both modality specific and modality independent components of individual perceptualasymmetry, the modality specific component accounting for more variance in participants asymmetry scores (35.7%) than the modality independent component (20.9%). Thus, one could speculate that the functional link between variation in *FOXP2* and language lateralization is into some extent mediated by activation in brain areas specifically activated during auditory processing, e.g. the primary auditory cortex. For example, in an fMRI study using the dichotic listening task, van den Noort, Specht, Rimol, Ersland, and Hugdahl (2008) showed bilateral activation in the superior and middle temporal gyrus, with larger and more extended areas of activation within the left posterior part of the superior temporal gyrus than within its right counterpart. Moreover, activations were found within the pre- and post-central gyrus and the supplementary motor area (related to motor activations due to verbal responses in thisversion of the task) as well as in the right and left middle frontal gyrus and in the superior frontal gyrus. In contrast, a recent review about the neurobiology of reading (Shaywitz & Shaywitz, 2008) identified three distinct neural subsystems relevant for tasks involving reading such as the visual half-field task used in the present study. These regions are the inferior frontal gyrus (Broca's area), relevant for articulation and word analysis, the parietotemporal cortex, relevant for word analysis, and the occipitotemporal cortex, relevant for word identification (Shaywitz & Shaywitz, 2008). Thus, it might be particularly interesting for future imaging genetics studies to look into the effects of *FOXP2* variation on activation in the superior and the middle temporal gyrus, since these areas show particularly pronounced activation on the auditorytask.

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