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Research report

KIAA0319 promoter DNA methylation predicts dichotic listening performance in forced-attention conditions

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ABSTRACT

Language lateralization is one of the most prominent examples of functional hemispheric asymmetries. Previous studies indicate a significant contribution of factors not related to DNA sequence variation on the development of language lateralization, but the molecular processes underlying this relation are unclear. The Brandler-Paracchini model of hemispheric asymmetries assumes that genes involved in the establishment of ciliogenesis and bodily asymmetries also affect functional hemispheric asymmetries. Thus, genes implicated in this model represent a key target for epigenetic modulation of language lateralization. Here, we analyzed DNA methylation in the *KIAA0319* (a gene involved in dyslexia and ciliogenesis) promoter region to investigate whether epigenetic markers of language lateralization can be identified in non-neuronal tissue. We found sex-specific effects of DNA methylation in single CpG sites on language lateralization in the forced-left (FL) and the forced-right (FR), but not on language lateralization in the non-forced (NF) condition of the dichotic listening task. These findings suggest that DNA methylation patterns in the *KIAA0319* promoter region might be associated with cognitive control processes that are necessary to perform well in the forced-attention conditions. Furthermore, the assumption of an association between genes involved in ciliogenesis and the ontogenesis of functional hemispheric asymmetries is supported.

1. Introduction

The vertebrate brain is divided into two hemispheres on the neuroanatomical level, which has wide implications on the functional level. Functional hemispheric asymmetries, i.e. performance differences between the left and right hemisphere, were initially thought to be uniquely human and determined by a single gene [1,2]. However, recent research indicates that hemispheric asymmetries are present in a large variety of species [3] and are influenced by multiple genetic [4] as well as multiple non-genetic factors [5]. Diverse aspects of hemispheric asymmetries have been shown to relate to a number of important aspects of cognitive neuroscience like language, perception, and emotional processing [6]. One of the most prominent examples of functional hemispheric asymmetries is language lateralization, the fact that there is a left-hemispheric dominance for language processing in 96% of strong right-handers (but only 73% of strong left-handers) [7]. Several studies have shown associations of language lateralization with genetic variants, for example in *KIAA0319* [8], *GRIN2B* [9], *CCKAR* [10], and *FOXP2* [11]. However, each of these candidates explains only a small fraction of interindividual variance. This is in line with a genetic linkage study indicating moderate heritability ($h^2 = 0.31$) of the trait [12]. For the dichotic listening task, the most widely used paradigm measuring language lateralization, it has been shown that cognitive control processes display moderate heritability whereas language lateralization itself shows low heritability at best [13]. These findings are in line with a significant contribution of non-genetic factors on language lateralization, but the molecular determinants are not well understood.

On the molecular level, environmental factors can affect cellular or behavioral phenotypes via epigenetic modifications modulating gene expression without changing the DNA sequence [14]. Among epigenetic modifications, DNA methylation is by far the best-characterized: The transfer of a methyl group to the C5 position of cytosine guanine (CpG) dinucleotides in a gene promoter typically results in reduced transcription of this gene [15]. DNA methylation has been shown to play a critical role in neurogenesis [16], synaptic transmission [17], learning and memory [18], but also in neurodegeneration [19] and mental disorders [20]. It has been proposed that DNA methylation in neuronal, but also in peripheral tissue reflects environmental influences and represents an informative biomarker for CNS-related traits [21]. As

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findings from genetic studies suggest a strong influence of non-genetic factors in the development of language lateralization, investigating promoter regions of relevant genes is promising to yield insights into its molecular determinants.

The Brandler-Paracchini model of hemispheric asymmetries assumes that genes involved in the establishment of ciliogenesis and bodily asymmetries also influence the early development of brain midline structures such as the *corpus callosum*, which then affects the development of reading ability or language lateralization [22,23]. In contrast to early single gene models of hemispheric asymmetries [1,2] the Brandler-Paracchini model is supported by molecular genetic evidence. Genes associated with handedness in subjects with and without dyslexia – a condition accompanied by reduced gray [24] and white matter asymmetries [25] – cause ciliopathies, heterotaxia, and situs inversus in knock-out mice [26]. Ciliopathies on the other hand result not only in altered bodily asymmetries but also in hypoplasia or agenesis of the *corpus callosum* [27]. These findings suggest that among the genes determining functional hemispheric asymmetries, some are also involved in the development of bodily asymmetries [26]. Moreover, candidate genes for dyslexia susceptibility like *DCDC2* [28,29], *DYX1C1* [30], and *KIAA0319* [31–34] are co-expressed in cilia [35]. A 77 kb spanning region on chromosome 6p22 including *ACOT13* and *TDP2* (formerly known as *THEM2* and *TTRAP*) and the first four exons of *KIAA0319* has repeatedly been associated with dyslexia [32] and reading ability in the general population [36,37]. More importantly, this chromosomal region has been directly associated with language dominance in healthy adults. Within the *KIAA0319/TDP2/ACOT13* region, a single nucleotide polymorphism (SNP; rs17243157 G/A; see Fig. 1) was significantly associated with left-lateralized activation of the posterior superior temporal sulcus (pSTS) during a reading and a speech listening task. Interestingly, those subjects bearing the gene variants associated with an elevated risk of dyslexia showed reduced pSTS asymmetry. The authors concluded that *KIAA0319* might be important for asymmetrical language processing in the pSTS [8].

Gene expression studies revealed that a risk haplotype for dyslexia within the *KIAA0319/TDP2/ACOT13* region (major allele of rs4504469 and rs2038137, minor allele of rs2143340, see Fig. 1) reduces *KIAA0319* gene expression by about 40% [33]. It was further shown that the minor allele (dyslexia risk allele) of rs9461045 in the region immediately upstream of *KIAA0319* (see Fig. 1) likely reduces *KIAA0319* gene expression [38]. *Kiaa0319* gene expression is essential for neocortex development in rats, as suppressed gene expression leads to impaired neuronal migration [33], reduced midsagittal corpus callosum volume [39], and impaired processing of complex auditory stimuli [40,41]. *KIAA0319* gene expression could thus represent an important step in the ontogenesis of dyslexia and altered hemispheric asymmetries.

KIAA0319 gene expression is not only regulated by DNA variations, but also by DNA methylation [42]. Recent studies have revealed some evidence for influences of DNA methylation on hemispheric asymmetries. For example, expression of numerous genes is considerably stronger in the right compared to the left fetal spinal cord at the starting point of rightward asymmetries in arm movements. Interestingly, asymmetries in gene expression coincided with opposed asymmetries in DNA methylation and miRNA expression [43]. The investigation of DNA methylation from buccal cells of healthy adults revealed that elevated DNA methylation in CpG stretches within the promoter region of *LRRTM1*, a promising candidate gene for handedness ontogenesis, is related to mixed-handedness, especially in females [44]. Taken together, these results strongly argue for a role of epigenetic processes in the development of hemispheric asymmetries.

We therefore investigated whether DNA methylation in the *KIAA0319* promoter region predicts language lateralization in healthy adults. The original dichotic listening task consists of consonant-vowel syllables presented to the left and right ear in homonym and dichotic stimulus pairs. As the subject is instructed to report the syllable he or she heard best in each trial, hemispheric dominance is assumed for the hemisphere contralateral to the more frequently reported – typically the right – ear. In later studies, two forced-attention conditions have been added in which the subject is instructed to only attend to input from the left ear and from the right ear, respectively. These additional conditions allow for the investigation of top-down attentional modulation [45]. The forced-left (FL) condition is suggested to induce a cognitive conflict, as bottom-up processing favors the more salient right ear, while top-down processing favors the left ear [46]. This makes the FL condition the most cognitively demanding, which also manifests in distinct activations in the left inferior prefrontal gyrus and caudate nucleus as revealed by fMRI [47]. In contrast, in the forced-right (FR) condition both bottom-up and top-down processing favor the more salient right ear. Thus, the two processing strategies are congruent, which reduces the need for cognitive control strategies compared to the FL condition [46].

In the context of the Brandler-Paracchini model of hemispheric asymmetries, we hypothesized that DNA methylation in the *KIAA0319* promoter region predicts language lateralization in the non-forced (NF) dichotic listening condition. However, *KIAA0319* is not only associated with language lateralization per se, but has been found to affect language-related cognitive skills [48,49] and executive functions [50]. Therefore, an involvement of DNA methylation in the *KIAA0319* promoter region in language lateralization in the forced-attention conditions (FL and FR) was also hypothesized.

2. Material and methods

2.1. Participants

59 healthy participants of Caucasian descent and free from neurological or psychiatric diseases took part in the study. The sample was

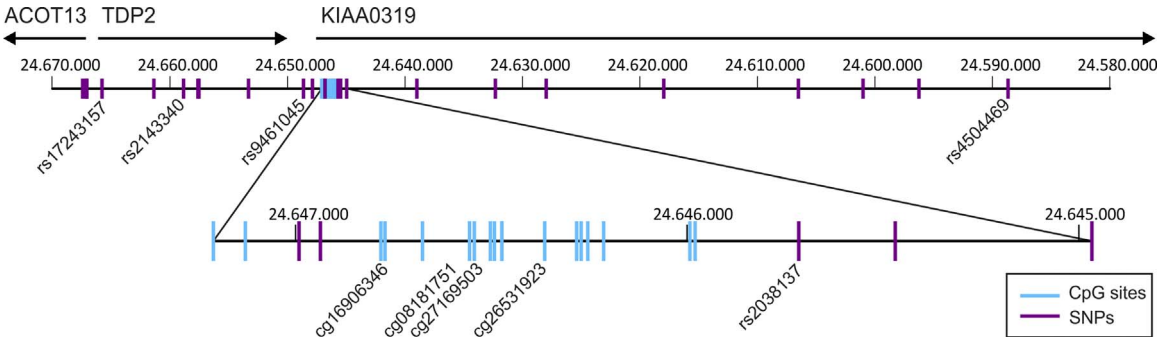

Fig. 1. The 77 kb *KIAA0319/TDP2/ACOT13* region associated with dyslexia by Francks et al. [32]. Depicted are all CpG sites analyzed in this study (turquoise) and SNPs associated with dyslexia in the studies by Dennis et al. [38], Francks et al. [32], Paracchini et al. [33], and Pinel et al. [8] (magenta). CpG sites and SNPs mentioned in the text are depicted with their corresponding names. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

composed of 30 men and 29 women with a mean age of 24.49 years (range 19–33 years, SD 3.02). Participants gave written informed consent and were treated in accordance with the declaration of Helsinki. The ethics committee of the Psychological Faculty at Ruhr University Bochum (Germany) approved the study procedure.

2.2. Dichotic listening task

Participants were tested with the iDichotic app for iOS [51,52] using an iPod touch (Apple Inc., Cupertino, CA) and headphones supplied with disposable sanitary headphone covers. The six consonant-vowel syllables (/ba/,/da/,/ga/,/ta/,/ka/,/pa/) were presented in all possible paired combinations, resulting in 30 dichotic and 6 homonym stimulus pairs. The stimuli were spoken by a male speaker and presented for 400–500 ms. The inter-stimulus interval was set to 4000 ms. During the inter-stimulus interval, participants responded by selecting one of the six syllables on the touchscreen of the iPod. The same set of stimuli was presented three times with different instructions. Participants first had to complete the non-forced condition (NF), in which they were instructed to report the syllable they heard best. The order of forced-left (FL) and forced-right (FR) conditions was randomized between participants. In the FL and FR condition, participants were instructed to only concentrate on the left or right ear, respectively, and report the syllable they heard on that ear. The order of syllables on the touchscreen was randomized between the three conditions.

2.3. DNA methylation

Buccal cells were brushed from the participants' oral mucosas using swabs. DNA was isolated using the blackPREP Swab DNA Kit (Analytik Jena, Germany) in accordance with the manufacturer's instructions. Bisulfite conversion was carried out on 500 ng of genomic DNA using the EpiTect Kit (Qiagen, Germany). Converted DNA was eluted in 10 µl elution buffer. Array analysis was carried out on the Illumina MethylationEPIC array using 4 µl of bisulfite-converted DNA [53].

2.4. Bioinformatics

Data were (pre-) processed using RStudio version 0.99.903 [54] and the RnBeads workflow [55]. Raw data were imported from signal intensity data. Probes with a corresponding detection p value > 0.01 were removed from the resulting RnBSet. Quality control excluded technical failures (such as bisulfite conversion efficiency and unspecific probe hybridization) or potential sample mix-ups. During preprocessing, probes overlapping with SNPs were removed from analysis. The Greedycut algorithm iteratively removed probes revealing impurity. The methylation β values (ranging from 0 to 1 as percentage of methylation) were normalized using the β-mixture quantile (BMIQ) method [56] to align type I and type II probe distributions and thereby reduce technical and systematic variability from the data. Non-CpG probes were removed during context-specific probe removal. DNA methylation can be allele-specific as a result of genetic imprinting, X-chromosome inactivation or in cis DNA variation [57]. Effects of X-chromosome inactivation were ruled out by removing all probes on sex chromosomes from the dataset. CpG sites showing overlap with known SNPs were also removed from the dataset. Annotation was conducted using the reference genome GRCh37 (hg19). As promoter regions were defined as 1.5 kb upstream and 0.5 kb downstream of transcription start sites, DNA methylation was investigated in 17 CpG sites within the *KIAA0319* promoter region spanning a chromosomal region of 2 kb (chr6: 24647883–24645884) within the *KIAA0319/TDP2/ACOT13* region associated with dyslexia [32]. No effect of genetic imprinting for *KIAA0319* was found in the current literature.

2.5. Statistical analysis

For the dichotic listening task, the percentage of correct reactions per ear in the dichotic trials were analyzed. Accuracy was analyzed using a 2 × 3 × 2 repeated-measures ANOVA with the within-subject factors Ear (left, right) and Condition (NF, FR, FL) and the between-subjects factor Sex (female, male). For each subject, an individual lateralization quotient (LQ) of accuracy was determined using the formula [(accuracy right ear − accuracy left ear)/(accuracy right ear + accuracy left ear) × 100] for each condition (NR, FR, and FL). Positive LQ values therefore indicate right ear advantage (left-hemispheric dominance), whereas negative LQ values indicate left ear advantage (right-hemispheric dominance). High absolute values indicate consistent language lateralization while low absolute values inconsistent language lateralization. For each condition, we conducted a linear step-wise regression analysis [31,58,59] with the individual% DNA methylation levels of all 17 CpG sites within the *KIAA0319* promoter as predictors and the corresponding accuracy LQ as the dependent variable. Since sex differences have also been revealed in autosomal DNA methylation [60,61] and due to cross-reactive probes co-hybridizing to the sex chromosomes [62], regression analyses were repeated for each sex separately. ANOVAs and linear regression analyses were calculated using IBM SPSS Statistics 20 (IBM, United States).

3. Results

3.1. Dichotic listening task

As expected, the mean LQ of accuracy was most negative in the FL condition, indicating a left ear advantage (−20.38, range: −76.92 to 46.15), and most positive in the FR condition indicating a right ear advantage (38.84, range: −17.65 to 85.19). In the NF condition, there was a less pronounced right ear advantage (6.85, range: −75.00 to 69.23). *T*-tests revealed no sex differences in mean LQs (NF: $t(57) = -0.68$, $p = 0.50$; FL: $t(47.46) = -1.80$, $p = 0.08$; FR: $t(57) = -0.33$, $p = 0.74$).

Both main factors (Ear: $F(1,57) = 17.04$, $p < 0.001$, partial $\eta^2 = 0.23$; Condition: $F(2,114) = 5.67$, $p < 0.01$, partial $\eta^2 = 0.09$) and the interaction Ear × Condition ($F(2,114) = 65.91$, $p < 0.001$, partial $\eta^2 = 0.54$) reached statistical significance in the ANOVA. Bonferroni-adjusted post-hoc tests revealed significant differences in performance between all conditions on both ears (see Fig. 2).

For the left ear, performance in the FL condition was significantly better than performance in the NF condition (9.83%, 95%-CI[5.54,

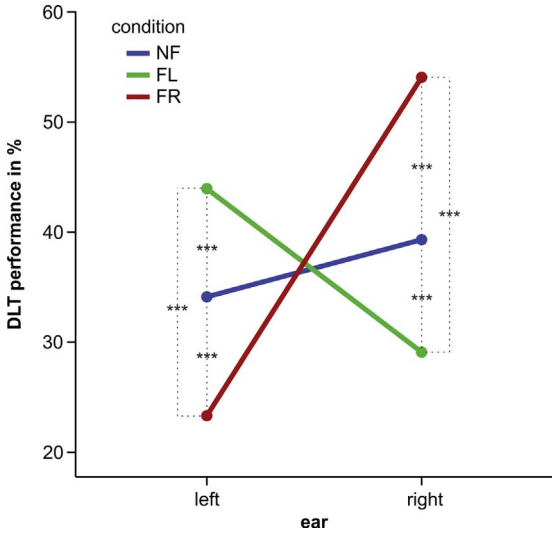

Fig. 2. Dichotic listening performance depending on ear and condition. *** p < 0.001.

14.12], $p < 0.001$) and the FR condition (20.62%, 95%-CI[14.78, 26.46], $p < 0.001$). Performance in the NF condition was also significantly better than performance in the FR condition (10.79%, 95%-CI [6.42, 15.34], $p < 0.001$). For the right ear, performance in the FR condition was significantly better than performance in the NF condition (14.75%, 95%-CI[10.24, 19.26], $p < 0.001$) and FR condition (24.97%, 95%-CI[18.38, 31.56], $p < 0.001$). Performance in the NF condition was also significantly better than performance in the FL condition (10.23%, 95%-CI[5.20, 15.25], $p < 0.001$).

There was a trend towards significance in the interaction Ear × Sex ($F(1,57) = 3.98$, $p = 0.051$, partial $\eta^2 = 0.07$). Bonferroni-adjusted post-hoc tests revealed a better performance of male in contrast to female subjects on the right ear (4.57%, 95%-CI[0.39, 8.75], $p < 0.05$), but no sex difference in left ear performance (2.16, 95%-CI[−1.49, 5.82], $p = 0.24$). However, the interactions Condition × Sex ($F(2,114) = 0.79$, $p = 0.46$, partial $\eta^2 = 0.01$) and Ear × Condition × Sex ($F(2,114) = 0.57$, $p = 0.57$, partial $\eta^2 = 0.01$) were non-significant.

3.2. DNA methylation

DNA methylation within the *KIAA0319* promoter did not significantly predict lateralization in the NR and FR condition (both $p > 0.05$). However, for the FL condition, the regression reached significance ($F(2,58) = 7.34$, $p < 0.01$) with R = 0.46 and $R^2 = 0.21$. In this analysis, two individual predictors reached statistical significance (cg16906346: β = 0.34, t = 2.81, $p < 0.01$; cg26531923: β = −0.27, $t = -2.24$, $p < 0.05$). Scatterplots for both significant CpG sites are displayed in Fig. 3(A, B; green regression lines).

Regression analyses were repeated for each sex separately. In women, similar to the results for the whole group, DNA methylation within the *KIAA0319* promoter only predicted lateralization in the FL condition ($F(2,58) = 6.42$, $p < 0.05$) with R = 0.44 and $R^2 = 0.19$, but not in the NR and FR condition (both $p > 0.05$). For the FL condition, only cg26531923 reached statistical significance (β = −0.44, $t = -2.53$, $p < 0.05$, see Fig. 3B). Although significantly predicting lateralization in the FL condition in the whole sample, cg16906346 was not significant in women (β = 0.25, $t = 1.15$, $p = 0.15$, see Fig. 3A). In contrast, for male participants DNA methylation within the *KIAA0319* promoter predicted lateralization in the FL ($F(2,29) = 7.23$, $p < 0.01$, R = 0.59 and $R^2 = 0.35$) and the FR condition ($F(1,29) = 9.81$, $p < 0.01$, R = 0.51 and $R^2 = 0.26$), but not in the NF condition ($p > 0.05$). In the FL condition, two individual predictors reached statistical significance (cg16906346: β = 0.48, $t = 3.12$, $p < 0.01$, see Fig. 3A; cg27169503: β = −0.35, $t = -2.22$, p < 0.05, see Fig. 3C). Although significantly predicting lateralization in the FL condition in the whole sample, cg26531923 was not significant in men (β = −0.14, t = −0.89, p = 0.38, see Fig. 3B). Thus, both CpG sites significantly predicting lateralization in the FL condition for the whole sample were only significant for either men or women in separate analyses (see Fig. 3A,B). In the FR condition, one individual predictor reached statistical significance in men (cg08181751: β = 0.51, $t = 3.13$, $p < 0.01$, see Fig. 3D). Chromosomal locations of all significant CpG sites are depicted in Fig. 1.

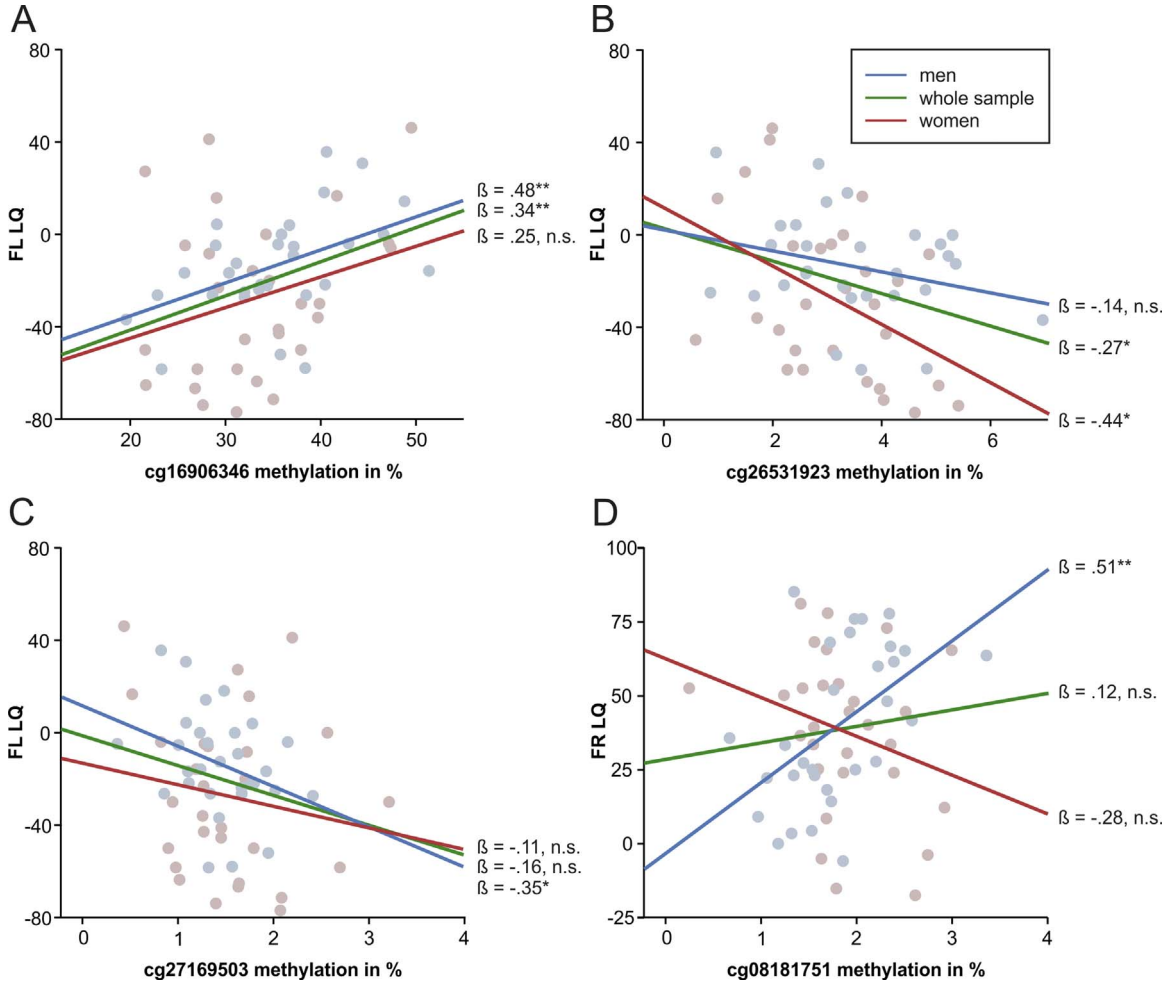

Fig. 3. Scatterplots of DNA methylation and corresponding LQs for the whole sample (green) and separately for men (blue) and women (red). * p < 0.05, ** p < 0.01, *** p < 0.001, n.s. non-significant. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

In the present study, we investigated DNA methylation within the promoter region of *KIAA0319* obtained from buccal cells and dichotic listening task performance in healthy adults. In accordance with previous research, the behavioral results indicated left-hemispheric language dominance that was enlarged in the FR and reversed in the FL condition [46]. Brandler and Paracchini [22] suggested that genes establishing bodily asymmetries via ciliogenesis also induce hemispheric asymmetries. Here we show that DNA methylation in the promoter region of *KIAA0319*, a gene involved in dyslexia and ciliogenesis, might be associated with language lateralization in the FL and FR conditions of the dichotic listening paradigm.

In contrast to hemispheric asymmetries, the ontogenesis of bodily asymmetries is fairly well investigated. Rotation of motile primary cilia causes a leftward nodal fluid flow that is detected by immotile primary cilia. This in turn induces stronger left-sided Nodal-cascade gene expression eventually forming the left-right axis of the body. Importantly, this process is not completely independent from the formation of brain asymmetries [63]. For example, patients suffering from *situs inversus*, a mirror reversal of visceral organs, showed more right-hemispheric language dominance as revealed by magnetoencephalography than controls [64], although no atypical language lateralization has been found using the dichotic listening paradigm [65]. However, *situs inversus* patients displayed atypical structural frontal and occipital hemispheric asymmetries in structural MRI [64,66].

The Brandler-Paracchini model of hemispheric asymmetries assumes a genetic relationship between ciliogenesis and hemispheric asymmetries. The transmembrane protein KIAA0319 has several polycystic kidney disease (PKD) domains [67] interactively regulating neurons and glial fibers during neuronal migration [68]. Ciliopathies are associated with the development of human PKDs [69] and knockout of polycystin-encoding genes or destabilization of PKD domains induce left-right asymmetry defects in mice [70,71]. *KIAA0319* is a target of the transcription factor TBR1 [72] whose orthologue *brachyury (T)* [73] partly determines left-right asymmetries in mice and *Xenopus laevis* [74–76]. Importantly, reduced gene expression of *Kiaa0319* results in reduced volume of the midsagittal *corpus callosum* [39].

Indeed, numerous studies report associations of language lateralization and corpus callosum size [77–79] or interhemispheric connectivity [80]. Moreover, language lateralization is altered in patients with acquired loss [81] as well as congenital absence of callosal fibers [82,83]. The CpG sites associated with language lateralization in our study are located nearby genetic variants associated with dyslexia [32] or *KIAA0319* gene expression regulation [33,38], which provides further support for the Brandler-Paracchini model [22,23]. Although not measured in this study, it can be suspected that gene expression of *KIAA0319* might not only be regulated by genetic variants associated with dyslexia but also by epigenetic modulation via DNA methylation and thereby affect language lateralization.

While the extent of language lateralization in the NF condition was not modulated by epigenetic variation, there was an effect of DNA methylation on lateralization in the FR condition for males and in the FL condition for both sexes. Ocklenburg et al. [13] found moderate heritability for the FL and FR conditions ($h^2 = 0.28$ and $h^2 = 0.36$, respectively) while the NF condition showed no heritability ($h^2 = 0.003$). This implies a role of non-genetic factors especially on the NF condition, but also on the FL and FR conditions. However, the opposite was the case for DNA methylation in *KIAA0319* with effects on FL and FR, but not on NF. Epigenetic factors determining language lateralization as measured by the NF condition might be related to genes other than *KIAA0319*.

Our results suggest that performance in the FL condition is influenced by sex-specific DNA methylation in the *KIAA0319* promoter region. For the whole sample, there were significant effects of two CpG sites on lateralization in the FL condition. However, separate analyses for men and women revealed that the effect for cg26531923 was only driven by the female subsample, while the effect for cg16906346 was only driven by the male subsample. In women, DNA methylation at cg26531923 was negatively related to lateralization in the FL condition. Thus, higher DNA methylation resulted in lower LQs and thus in a more pronounced left ear advantage and enhanced FL performance in women. In men, DNA methylation at cg16906346 and cg27169503 was associated with lateralization in the FL condition; however, the effects were of opposite directions with a positive relationship between cg16906346 DNA methylation and FL performance and a negative relationship between cg27169503 DNA methylation and FL performance.

For lateralization in the FR condition, there was no significant effect of DNA methylation in women, but a highly significant association of cg08181751 in men with stronger DNA methylation resulting in a more pronounced right ear advantage. Although non-significant, the data for female participants rather show the reversed pattern, a negative relationship between DNA methylation at cg08181751 and lateralization in the FR condition.

Overall, DNA methylation in the *KIAA0319* promoter region predicted language lateralization in the forced conditions, but not in the original NF condition. DNA methylation patterns in the *KIAA0319* promoter region might therefore rather be associated with cognitive control processes than lateralized language perception per se. This is in line with the fact that the strongest effects were found in the FL condition, which requires the highest cognitive demand [46,47], and earlier reports of *KIAA0319* influencing language-related cognitive functions [48–50].

The most obvious methodological limitation of this study is the use of peripheral tissue for the investigation of a CNS-related phenotype. It was recently concluded that the investigation of DNA methylation from blood cells is eligible to study CNS-related phenotypes in terms of “epigenetic signatures” rather than mechanistic explanations [84]. A comparison of DNA methylation in buccal, brain, and blood cells revealed that buccal cells show greater overlap with brain cells than blood cells, thus providing a more suitable biomarker for brain phenotypes [85]. It is of note that for cg16906346, a very high correlation ($r > 0.91$) was observed between blood and brain DNA methylation levels [86].

The current study should be complemented with additional approaches in subsequent research. Future studies should extend to imaging epigenetics, which has already revealed insight in the ontogenesis of other CNS-related phenotypes [87]. Furthermore, schizophrenia patients experiencing auditory hallucinations could be compared with healthy adults, as a reduced right ear advantage is a strong effect as revealed by meta-analysis [88]. Interestingly, rare genetic variants leading to agenesis of the *corpus callosum* can also affect DNA methylation and lead to deafness and the Andermann syndrome characterized by agenesis of the *corpus callosum*, peripheral neuropathy and psychoses [89]. Furthermore, dysregulations in DNA methylation have been found in brain [90,91], blood [92–94], and buccal cells [95] of schizophrenia patients. Comparative approaches could add substantially to the existing literature, since the human brain seems to be more responsive to environmental pressure than the chimpanzee brain [96].

5. Conclusions

Taken together, our data show that DNA methylation within the *KIAA0319* promoter region represents an epigenetic marker or signature of language lateralization in non-neuronal tissue. This study supports the idea of a multifactorial model for the ontogenesis of language lateralization with a multitude of genetic and epigenetic effects each exerting small effects on the phenotype. Our findings provide insight into the ontogenesis of hemispheric asymmetries and support the Brandler-Paracchini model, indicating an association between genes involved in ciliogenesis and the ontogenesis of functional hemispheric asymmetries.

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Competing interests statement

The authors have no competing interests to declare.

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