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Schizotypy and altered hemispheric asymmetries: The role of cilia genes

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ABSTRACT

Schizophrenia patients have a higher probability of altered structural and functional differences between the left and right hemisphere. Schizotypy as its nonclinical manifestation has been related to a higher incidence of non-right-handedness and atypical right-hemispheric language dominance. It has been suggested that genes involved in cilia function might link brain asymmetry and neurodevelopmental disorders. We assessed DNA methylation in the promoter regions of seven candidate genes involved in cilia function and psychiatric disorders from buccal cells and investigated their association with schizotypy and language lateralization in 60 healthy adults. Moreover, we determined microstructural properties of the *planum temporale* in a subsample of 52 subjects using neurite orientation dispersion and density imaging (NODDI). We found a significant association between schizotypy and DNA methylation in the *AHI1* promoter region. Moreover, *AHI1* DNA methylation significantly predicted language lateralization and asymmetry in estimated *planum temporale* neurite density. Finally, stronger leftward asymmetry in estimated neurite density was associated with a more pronounced right ear advantage (left hemisphere dominance) in the forced-right condition of the dichotic listening task, measuring attentional modulation of language lateralization. Our results are in line with a shared molecular basis of schizotypy and functional hemispheric asymmetries that is based on cilia function.

1. Introduction

An alteration of structural or functional differences between the cerebral hemispheres (atypical laterality) is a consistent finding in schizophrenia (Ocklenburg and Güntürkün, 2018). Patients often show reduction or reversal of the typical macrostructural leftward *planum temporale* asymmetry (Sommer et al., 2001), are more often left-handed (Hirnstein and Hugdahl, 2014) and show reduced left-hemispheric language lateralization compared to healthy controls (Ocklenburg et al., 2013c). Whereas schizophrenia has a lifetime prevalence of below 1%, its symptomatology lies on a continuum with schizotypy as a nonclinical continuous personality trait (Mason, 2015). High schizotypy has been associated with non-right-handedness (Schürhoff et al., 2008; Somers et al., 2009) and reduced language

Abbreviations: AHI1, Abelson helper integration site 1; AMICO, Accelerated Microstructure Imaging via Convex Optimization; BDNF, brain-derived neurotrophic factor; CA, constricted affect (SPQ-G subscale); CCKAR, cholecystokinin A receptor; CNS, Central nervous system; COMT, catechol-O-methyltransferase; DCDC2, doublecortin domain containing 2; DISC1, DISC1 scaffold protein; DYX1C1, dyslexia susceptibility 1 candidate 1; EB, eccentric behavior (SPQ-G subscale); EHI, Edinburgh handedness inventory; FDT, FMRIB's Diffusion Toolbox; FL, forced-left condition (of the dichotic listening task); fMRI, functional magnetic resonance imaging; FOXP2, forkhead box P2; FR, forced-right condition (of the dichotic listening task); FSL, FMRIB Software Library; fTCD, Functional transcranial Doppler sonography; GRIN2B, glutamate ionotropic receptor NMDA type subunit 2B; IMAGE-CpG, Iowa Methylation Array Graphing for Experimental Comparison of Peripheral tissue & Gray matter; INVF, intraneurite volume fraction; IR, ideas of reference (SPQ-G subscale); LQ, laterality quotient; MT, magical thinking (SPQ-G subscale); NCF, no close friends (SPQ-G subscale); NF, non-forced condition (of the dichotic listening task); NODAL, nodal growth differentiation factor; NODDI, Neurite orientation dispersion and density imaging; ODI, orientation dispersion index; OS, odd speech (SPQ-G subscale); PCM1, pericentriolar material 1; PCNT, pericentrin; PCSK6, proprotein convertase subtilisin/kexin type 6; PKD, polycystic kidney disease; PLP1, proteolipid protein 1; S, suspiciousness (SPQ-G subscale); SA, social anxiety (SPQ-G subscale); SPQ-G, German version of the Schizotypal personality questionnaire; TrkB, tyrosine kinase receptor B; TSC1, TSC complex subunit 1; UPE, unusual perceptual experiences (SPQ-G subscale)

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lateralization (Poreh et al., 1993). Molecular studies revealed evidence for a shared genetic basis of schizophrenia and language lateralization (e.g. in *FOXP2* (Pinel et al., 2012; Ocklenburg et al., 2013b; McCarthy-Jones et al., 2014), *GRIN2B* (Cherlyn et al., 2010; Ocklenburg et al., 2011), *CCKAR* (Ocklenburg et al., 2013a) and *PLP1* (Qin et al., 2005; Ocklenburg et al., 2018b)) and handedness (e.g. *LRRTM1* (Francks et al., 2007; Leach et al., 2014), *COMT* (Savitz et al., 2007; González-Castro et al., 2016) and *PCSK6* (Scerri et al., 2011; Arning et al., 2013; Brandler et al., 2013; Robinson et al., 2016)).

Interestingly, *PCSK6* also plays a critical role in the development of visceral asymmetries (Norris, 2012). Moreover, genes involved in the formation of cilia, rotating organelles that serve fluid movement inducing a leftward flow of NODAL resulting in left-right axis patterning during embryogenesis, are overrepresented in genes associated with handedness (Brandler et al., 2013). Thus, it has been suggested that molecular mechanisms establishing visceral asymmetry and ciliogenesis might also influence the development of brain midline structures, thereby affecting asymmetries of brain and behavior (Brandler and Paracchini, 2014). Trulioff et al. (2017) reviewed the evidence for proteins involved in cilia function also being associated with psychiatric disorders. Specifically, DISC1, PCM1, PCNT, and AHI1 are involved in cardiovascular asymmetry and schizophrenia, while *TSC1* is involved in visceral asymmetry and autism spectrum disorder and DCDC2 and DYX1C1 are associated with visceral asymmetry and dyslexia (Trulioff et al., 2017).

In addition to genetic variation, gene expression studies in human fetal CNS tissue (de Kovel et al., 2017; Ocklenburg et al., 2017; de Kovel et al., 2018) have suggested a role of epigenetic regulation (Ocklenburg et al., 2017) in the ontogenesis of hemispheric asymmetries. Epigenetic markers of functional hemispheric asymmetries have recently been reported in non-neuronal tissue (Leach et al., 2014; Schmitz et al., 2018a,b, 2019b). As epigenetic regulation does not affect behavior directly, but likely via altered brain structure or function, imaging epigenetic approaches have been successful in revealing insights on neurodevelopment (Lista et al., 2013) and specifically in the context of the development of hemispheric asymmetries (Schmitz et al., 2017). For example, in an epigenome-wide analysis, variance in DNA methylation as detected per principal component analysis has been associated with right, but not left corticospinal shape in infants (Sparrow et al., 2016). Here, we conducted an epigenetic imaging approach specifically focusing on the *planum temporale*, which is characterized by pronounced microstructural asymmetry in healthy participants (Buxhoeveden et al., 2001), which is reduced or reversed in schizophrenia patients (Chance, 2014). However, *post mortem* studies naturally do not allow for the investigation of structure function relationships. Recent advances in neuroimaging allow for *in vivo* quantification of neurite morphology. Neurite orientation dispersion and density imaging (NODDI) is a diffusion MRI technique estimating neurite density (intraneurite volume fraction, INVF) and neurite tortuosity (orientation dispersion index, ODI) (Zhang et al., 2012) as validated in animal (Jespersen et al., 2007; Jespersen et al., 2010) and human CNS tissue (Grussu et al., 2017). Recently, we could show that in line with *post mortem* studies INVF is strongly leftward asymmetric in the auditory association cortex including the *planum temporale* (Schmitz et al., 2019a). Moreover, it was shown that the extent of *planum temporale* INVF asymmetry predicts N1 latency in a dichotic listening paradigm (Ocklenburg et al., 2018a), suggesting that left-hemispheric dominance in speech processing is based on *planum temporale* microstructure asymmetry.

Here, we tested healthy participants phenotyped with schizotypal personality scores and language lateralization. Microstructural *planum temporale* asymmetry was determined using NODDI. First, we hypothesized that DNA methylation in promoter regions of genes involved in visceral asymmetry and psychiatric disorders predicts schizotypy in healthy participants (see Figure 1).

Since *DISC1, PCM1, PCNT*, and *AHI1* have been directly associated with schizophrenia (Trulioff et al., 2017), we expected an effect of these genes specifically. Second, as language lateralization is reduced in high schizotypy individuals (Poreh et al., 1993), DNA methylation in promoter regions of genes showing an association with schizotypy was also expected to predict language lateralization. Third, based on the association between language lateralization and *planum temporale* microstructural asymmetry (Ocklenburg et al., 2018a), DNA methylation in promoter regions of genes showing an association with schizotypy was also expected to predict *planum temporale* microstructural asymmetry. Fourth, based on behavioral findings of reduced language lateralization in participants with high schizotypy scores (Poreh et al., 1993), asymmetry in *planum temporale* microstructure was hypothesized to correlate positively with schizotypy scores (as negative asymmetry values indicate leftward asymmetry, which is assumed to be associated with low schizotypy scores). Fifth, asymmetry in *planum temporale* microstructure was expected to correlate negatively with language lateralization in the dichotic listening task (as positive dichotic listening scores indicate a left hemisphere dominance, which is assumed to be associated with leftward asymmetry of *planum temporale* microstructure).

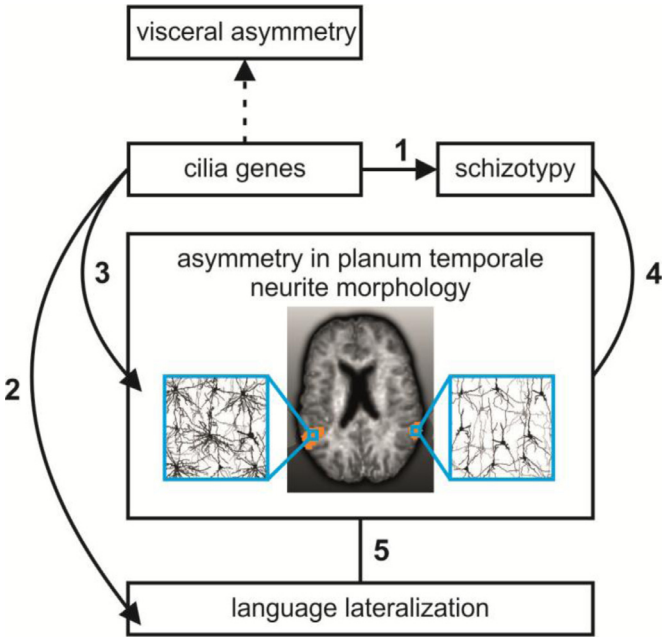

Fig. 1. Hypothesized associations between cilia genes, schizotypal personality scores, asymmetry in *planum temporale* neurite morphology, and language lateralization as determined by the dichotic listening task. Cilia genes are involved in visceral asymmetry (not measured here) and are hypothesized to predict (indicated by arrows) schizotypy scores (hypothesis 1), language lateralization (hypothesis 2) and *planum temporale* microstructural asymmetry (hypothesis 3). Moreover, *planum temporale* microstructural asymmetry was hypothesized to correlate (indicated by lines) with schizotypy scores (hypothesis 4) and language lateralization (hypothesis 5).

2. Methods

2.1. Participants

Sixty participants (30 female) of German descent (mean age 24.4 years, SD 3.1 years) free from psychiatric or neurological disorders and with normal or corrected to normal vision were tested. One participant was excluded from the dichotic listening task due to a hearing deficit. 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 Faculty of Psychology at Ruhr University Bochum, Germany.

2.2. Behavioral assessment

All participants completed the German version of the Schizotypal personality questionnaire (SPQ-G) (Raine, 1991). Participants were selected for consistent left- or right-handedness as determined by the Edinburgh handedness inventory laterality quotient (EHI LQ) (Oldfield, 1971). Thirty participants (15 female) were consistently left-handed (EHI LQ M = −88.2, SD = 13.6) and thirty participants (15 female) were consistently right-handed (EHI LQ M = 87.6, SD = 16.3). Language lateralization was determined using the *iDichotic* app (Bless et al., 2013), presenting consonant-vowel syllables in homonym and dichotic stimulus pairs to the left and right ear. In the non-forced condition (NF), participants were instructed to select the syllable they heard best. In the forced-left (FL) and forced-right (FR) conditions, participants were instructed to specifically select the syllable presented to the respective ear.

2.3. DNA methylation

DNA methylation was analyzed from buccal samples. DNA was isolated using the blackPREP Swab DNA Kit (Analytik Jena, Germany). Genomic DNA was bisulfite converted using the EpiTect Kit (Qiagen, Germany). The Illumina MethylationEPIC array was used for array analysis. Data were analyzed using RStudio version 0.99.903 and the RnBeads workflow (Assenov et al., 2014) as described previously (Schmitz et al., 2018b,a). Promoter regions were defined as 1.5 kb upstream and 0.5 kb downstream of transcription start sites (see Table 1 for the definition of promoter regions and Table 2 for all tested individual CpG sites). No effect of genetic imprinting was found in the literature for *DISC1* (Hayesmoore et al., 2008), *PCM1, PCNT, AHI1, TSC1, DCDC2*, or *DYX1C1*.

As DNA methylation is highly tissue-specific, it is unclear if our data, collected from buccal samples, reflect DNA methylation in brain tissue. The reasoning behind using peripheral tissue is the suggestion that it still predicts interindividual variation of DNA methylation in brain tissue (Hannon et al., 2015). Thus, the results obtained in the current study are interpreted as peripheral epigenetic signatures (Freytag et al., 2017) of schizotypy, language lateralization and microstructural *planum temporale* asymmetry.

Moreover, we used the IMAGE-CpG (Iowa Methylation Array Graphing for Experimental Comparison of Peripheral tissue & Gray matter) tool to determine the correlation coefficient between DNA methylation in buccal cells and brain tissue for significant CpG sites. This tool offers Spearman's rho correlation coefficients and p-values for CpG sites on the Illumina MethylationEPIC array between different peripheral tissues (blood, saliva, buccal cells) as well as gray matter tissue that had been removed during surgical epilepsy treatment in 13 patients (Braun et al., 2019b,Braun et al., 2019).

2.4. Neuroimaging

Imaging data were acquired for 52 participants at the University Hospital Bergmannsheil in Bochum, Germany, using a Philips 3T Achieva scanner equipped with a 32-channel head coil.

To enable gray and white matter segmentation and identification of anatomical landmarks, T1-weighted high-resolution anatomical images were acquired (MP-RAGE, repetition time 8.2 ms, echo time 3.7 ms, flip angle 8°, 220 slices, matrix size 240 × 240, voxel size = 1 × 1 × 1 mm).

Diffusion-weighted images were acquired using echo planar imaging (repetition time 8.2 s, echo time 95 ms, flip angle 90°, 60 slices, matrix size 112 × 112, voxel size 2 × 2 × 2 mm). We employed a multi-shell, high-angular-resolution scheme using diffusion-weighted images with b-values of 1000, 1800, and 2500 s/mm^2, measured along 20, 40, and 60 uniformly distributed directions. Diffusion directions within and between shells were generated orthogonal to each other using the MASSIVE toolbox. Eight volumes were acquired with no diffusion weighting (b = 0 s/mm^2) for anatomical reference for motion correction and computation of NODDI coefficients.

Cortical surfaces of T1-weighted images were reconstructed using FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu) (Dale et al., 1999; Fischl et al., 1999). Preprocessing included skull stripping, gray and white matter segmentation and cortical surface reconstruction and inflation. Each slice was checked for inaccuracies and manually edited if necessary. The *planum temporale* was defined per hemisphere from the T1-weighted images using an automatic segmentation procedure implemented in FreeSurfer. The parcellation scheme was based on the Destrieux atlas (Destrieux et al., 2010).

Preprocessing of diffusion images was performed using FMRIB's Diffusion Toolbox (FDT) in FMRIB Software Library (FSL) version 5.0.7. Preprocessing was performed as described previously (Genç et al., 2018). NODDI coefficients were computed using the AMICO toolbox (Daducci et al., 2015). NODDI distinguishes three tissue compartments (intraneurite, extraneurite, and cerebrospinal environments). This results in estimates for neurite density (INVF) and neurite orientation dispersion (ODI) (Zhang et al., 2012). A detailed description of NODDI coefficients and their histological validation can be found in the corresponding literature (Jespersen et al., 2007; Jespersen et al., 2010; Zhang et al., 2012; Grussu et al., 2017).

The *planum temporale* was transformed into the native space of the diffusion-weighted images to compute gray matter NODDI coefficients (INVF, ODI). Both were computed voxel-wise and averaged for the left and right *planum temporale*, respectively. LQs were calculated by the formula LQ = [(right – left)/(right + left)] × 100.

2.5. Statistical analysis

Independent t-tests were calculated to test for sex and handedness effects on SPQ-G scores. We conducted seven Bonferroni-corrected stepwise linear regression analyses with all CpG sites within the respective promoter region (*DISC1, PCM1, PCNT, AHI1, TSC1, DCDC2, DYX1C1*) as independent variables and SPQ-G score as the dependent variable ($\alpha = 0.007$). In order to test whether specific subscales of the SPQ-G drove the significant effect, nine Bonferroni-corrected regression analyses were performed with DNA methylation in the *AHI1* promoter region as independent variables and the respective SPQ-G subscale (IR, SA, MT, UPE, EB, NCF, OS, CA, and S) as the dependent variable ($\alpha = 0.0055$).

Table 1
Promoter regions of examined genes with chromosomal locations, ENSEMBL gene ID and number of tested CpG sites.

Gene	Chromosome	Start of promoter region	End of promoter region	ENSEMBL gene ID	Number of CpG sites tested within the promoter region
DISC1	1	231761061	231763060	ENSG00000162946	12
PCM1	8	17778849	17780848	ENSG00000078674	10
PCNT	21	47742536	47744535	ENSG00000160299	14
AHI1	6	135818415	135820414	ENSG00000135541	14
TSC1	9	135819521	135821520	ENSG00000165699	12
DCDC2	6	24357781	24359780	ENSG00000146038	10
DYX1C1	15	55799933	55801932	ENSG00000256061	3

Table 2
Examined CpG sites with chromosomal locations and results from regression analyses.

Gene	CpG ID	Chromosome	Start	End	Association
DISC1	cg24430578	1	231761688	231761689	-
DISC1	cg00346898	1	231761721	231761722	-
DISC1	cg14816899	1	231761832	231761833	-
DISC1	cg13782866	1	231761845	231761846	-
DISC1	cg24499839	1	231762238	231762239	-
DISC1	cg03987748	1	231762359	231762360	-
DISC1	cg08838517	1	231762368	231762369	-
DISC1	cg09305898	1	231762372	231762373	-
DISC1	cg16178998	1	231762459	231762460	-
DISC1	cg06756369	1	231762664	231762665	-
DISC1	cg18565479	1	231762737	231762738	-
DISC1	cg27584828	1	231762962	231762963	-
PCM1	cg13954385	8	17779923	17779924	-
PCM1	cg09094615	8	17779997	17779998	-
PCM1	cg04467958	8	17780063	17780064	-
PCM1	cg08963608	8	17780106	17780107	-
PCM1	cg19034708	8	17780168	17780169	-
PCM1	cg17918875	8	17780190	17780191	-
PCM1	cg26692822	8	17780298	17780299	-
PCM1	cg01642733	8	17780317	17780318	-
PCM1	cg20533955	8	17780351	17780352	-
PCM1	cg11050116	8	17780536	17780537	-
PCNT	cg24358815	21	47742804	47742805	-
PCNT	cg16319213	21	47742881	47742882	-
PCNT	cg10486505	21	47743117	47743118	-
PCNT	cg15467615	21	47743775	47743776	-
PCNT	cg03030524	21	47743819	47743820	-
PCNT	cg11967727	21	47743836	47743837	-
PCNT	cg16252642	21	47743847	47743848	-
PCNT	cg02835038	21	47743854	47743855	-
PCNT	cg12253754	21	47743907	47743908	-
PCNT	cg02503257	21	47743914	47743915	-
PCNT	cg12148368	21	47743931	47743932	-
PCNT	cg05977990	21	47744112	47744113	-
PCNT	cg25110234	21	47744248	47744249	-
PCNT	cg06468476	21	47744347	47744348	-
AHI1	cg21817183	6	135818446	135818447	-
AHI1	cg25946909	6	135818502	135818503	-
AHI1	cg21276217	6	135818529	135818530	SPQ-G OS:ß = -0.35, $p < .0055$
AHI1	cg21071512	6	135818740	135818741	-
AHI1	cg14291549	6	135818752	135818753	NF LQ:ß = 0.38, $p < .017$
AHI1	cg23945725	6	135818818	135818819	INVF LQ:ß = 0.32, $p < .025$
AHI1	cg16085178	6	135818824	135818825	FR LQ:ß = 0.36, $p < .017$
AHI1	cg08231603	6	135818959	135818960	-
AHI1	cg00664135	6	135819137	135819138	SPQ-G EB:\ß = 0.35, $p < .0055$
AHI1	cg13150400	6	135819157	135819158	-
AHI1	cg06183947	6	135819352	135819353	FR LQ:ß = -0.35, $p < .017$
AHI1	cg12164973	6	135819354	135819355	-
AHI1	cg21539510	6	135819589	135819590	-
AHI1	cg20128181	6	135819596	135819597	SPQ-G total score:ß = -0.40, $p < .007$ SPQ-G IR:ß = -0.39, $p < .0055$ SPQ-G S:ß = -0.41, $p < .0055$ NF LQ:ß = -0.26, $p = .038$
TSC1	cg07738800	9	135819856	135819857	-
TSC1	cg11295002	9	135819984	135819985	-
TSC1	cg12207024	9	135820109	135820110	-
TSC1	cg00425865	9	135820111	135820112	-
TSC1	cg12146158	9	135820115	135820116	-
TSC1	cg14350545	9	135820463	135820464	-
TSC1	cg19350728	9	135820526	135820527	-
TSC1	cg14061503	9	135820653	135820654	-
TSC1	cg19393006	9	135820767	135820768	-
TSC1	cg05233902	9	135820847	135820848	-
TSC1	cg27495603	9	135820898	135820899	-
TSC1	cg06221539	9	135821170	135821171	-
DCDC2	cg14069965	6	24357816	24357817	-
DCDC2	cg03960072	6	24357985	24357986	-
DCDC2	cg04515001	6	24358236	24358237	-
DCDC2	cg10329683	6	24358298	24358299	-
DCDC2	cg05347898	6	24358304	24358305	-
DCDC2	cg16306115	6	24358306	24358307	-
DCDC2	cg07791578	6	24358308	24358309	-
DCDC2	cg07054208	6	24358566	24358567	-
DCDC2	cg04945158	6	24358681	24358682	-

(*continued on next page*)

Table 2 (*continued*)

Gene	CpG ID	Chromosome	Start	End	Association
DCDC2	cg16427109	6	24358683	24358684	-
DYX1C1	cg14215625	15	55800831	55800832	-
DYX1C1	cg08433095	15	55801069	55801070	-
DYX1C1	cg12643702	15	55801378	55801379	-

The behavioral data for the dichotic listening task have been described previously (Schmitz et al., 2018b). Accuracy (percentage of correct reactions) was analyzed using a 2 × 3 × 2 repeated-measures ANOVA with the within-subject factors ear (left, right) and condition (NF, FL, FR) and the between-subject factor sex (female, male). For each of the three conditions, an accuracy LQ was calculated to determine language lateralization (NF LQ, FL LQ, FR LQ). We conducted three Bonferroni-corrected stepwise linear regression analyses with all CpG sites within the *AHI1* promoter region as independent variables and NF LQ, FL LQ, and FR LQ as dependent variables ($\alpha = 0.017$).

One-sample t-tests were conducted to test whether INVF LQ and ODI LQ differed significantly from zero. Independent t-tests were calculated to test for sex and handedness effects. We conducted two Bonferroni-corrected stepwise linear regression analyses with all CpG sites within the *AHI1* promoter region as independent variables and INVF LQ and ODI LQ as dependent variables ($\alpha = 0.025$).

Eight Bonferroni-corrected bivariate Pearson correlations were performed between INVF LQ and ODI LQ with schizotypy, NF LQ, FL LQ, and FR LQ ($\alpha = 0.00625$).

Statistical analysis was performed using IBM SPSS Statistics 20 (IBM, United States).

3. Results

3.1. DNA methylation and schizotypy

SPQ-G scores ranged from 0 to 38 (M = 13.47, SD = 8.70). T-tests revealed no sex ($t(58) = -1.41$, $p = .165$) or handedness ($t(58) = 1.10$, $p = .276$) effects.

DNA methylation in the *DISC1, PCM1, PCNT, TSC1, DCDC2*, and *DYX1C1* promoter regions did not significantly predict schizotypy scores (all $p > .007$). DNA methylation in the *AHI1* promoter region significantly predicted schizotypy ($F_{(2,59)} = 6.79$, $p < .007$). Two predictors reached significance: one single CpG site in the *AHI1* promoter region (cg20128181: ß = -0.40, $p < .007$, see Fig. 2) and sex, which, however, did not survive correction for multiple comparisons (ß = 0.25, $p = .046$).

The IMAGE-CpG tool revealed a positive correlation coefficient between DNA methylation in buccal cells and brain tissue for cg20128181 in the promoter region of *AHI1* ($r = 0.4$, $p = .07$).

Stepwise regression analyses were repeated with DNA methylation in the *AHI1* promoter region and SPQ-G subscales. The regression did not reach Bonferroni-corrected significance for five subscales (SA, MT, UPE, NCF, CA; all $p > .0055$). The regression reached significance for IR ($F_{(2,57)} = 8.54$, $p < .0055$; cg20128181: ß = -0.39, $p < .0055$), EB ($F_{(3,56)} = 5.24$, $p < .0055$; cg00664135: ß = 0.35, $p < .0055$), OS ($F_{(3,56)} = 5.32$, $p < .0055$; cg21276217: ß = -0.35, $p < .0055$), and S ($F_{(1,58)} = 12.02$, $p < .0055$; cg20128181: ß = -0.41, $p < .0055$). Thus, the effect of cg20128181 in the promoter region of *AHI1* was likely driven by subscales IR (ideas of reference) and S (suspiciousness).

3.2. DNA methylation in the AHI1 promoter region and language lateralization

The behavioral results for the *iDichotic* app have been described elsewhere (Schmitz et al., 2018b). In brief, there were significant main effects of ear and condition as well as a significant ear × condition interaction, indicating a right ear advantage in the NF condition that was enlarged in the FR condition and reversed in the FL condition.

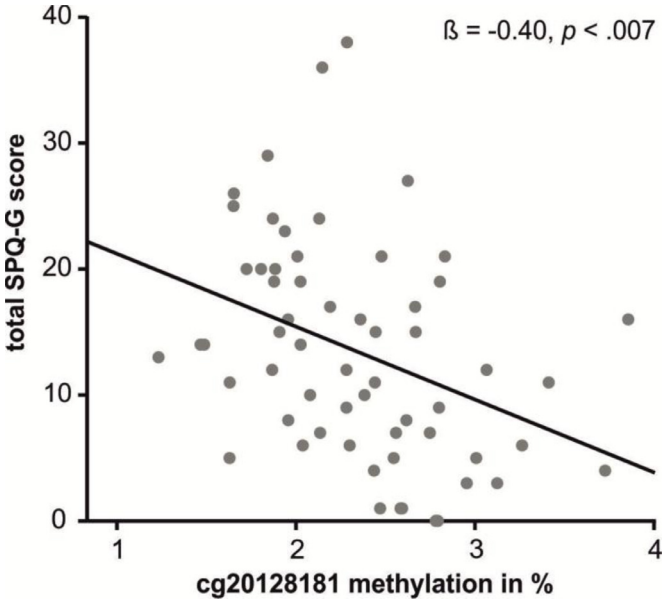

Fig. 2. *Scatterplot of AHI1 DNA methylation and corresponding total SPQ-G score.* There is a negative association between cg20128181 DNA methylation and schizotypy scores.

DNA methylation in the *AHI1* promoter region significantly predicted NF LQ ($F_{(2,56)} = 6.51$, $p < .017$). Two CpG sites in the promoter region of *AHI1* reached significance (cg14291549: ß = 0.38, $p < .017$, see Fig. 3A), however, one did not survive correction for multiple comparisons (cg20128181: ß = -0.26, $p = .038$). DNA methylation did not significantly predict FL LQ ($p > .017$), but the regression reached significance for FR LQ ($F_{(2,56)} = 7.30$, $p < .017$). Two CpG sites reached significance (cg06183947: ß = -0.35, $p < .017$, see Fig. 3B; cg16085178: ß = 0.36, $p < .017$, see Fig. 3C).

However, IMAGE-CpG revealed a non-significant negative correlation coefficient between DNA methylation in buccal cells and brain tissue for cg14291549 ($r = -0.2$, $p = .20$) and no correlation for cg16085178 ($r = 0.03$, $p = .89$). There were no correlation data available for cg06183947.

3.3. DNA methylation in the AHI1 promoter region and asymmetry in planum temporale microstructure

T-tests revealed that INVF LQ was not significantly different from zero (M = -0.32, SD = 2.77; $t_{(51)} = -0.85$, $p = .402$), while ODI LQ was significantly negative (M = -1.75, SD = 3.13; $t_{(51)} = -4.04$, $p < .001$), indicating stronger left- than right-hemispheric ODI. *T*-tests revealed no sex differences (INVF LQ: $t_{(50)} = 0.23$, $p = .818$; ODI LQ: $t_{(50)} = 0.35$, $p = .730$). *T*-tests revealed a nominally significant handedness effect in INVF LQ ($t(50) = -2.02$, $p = .049$; left-handers: M = -1.16, SD = 2.59; right-handers: M = 0.35, SD = 2.76), but no difference in ODI LQ ($t_{(50)} = -0.91$, $p = .365$).

DNA methylation in the *AHI1* promoter region significantly predicted INVF LQ ($F_{(1,50)} = 5.81$, $p < .025$). One CpG site reached

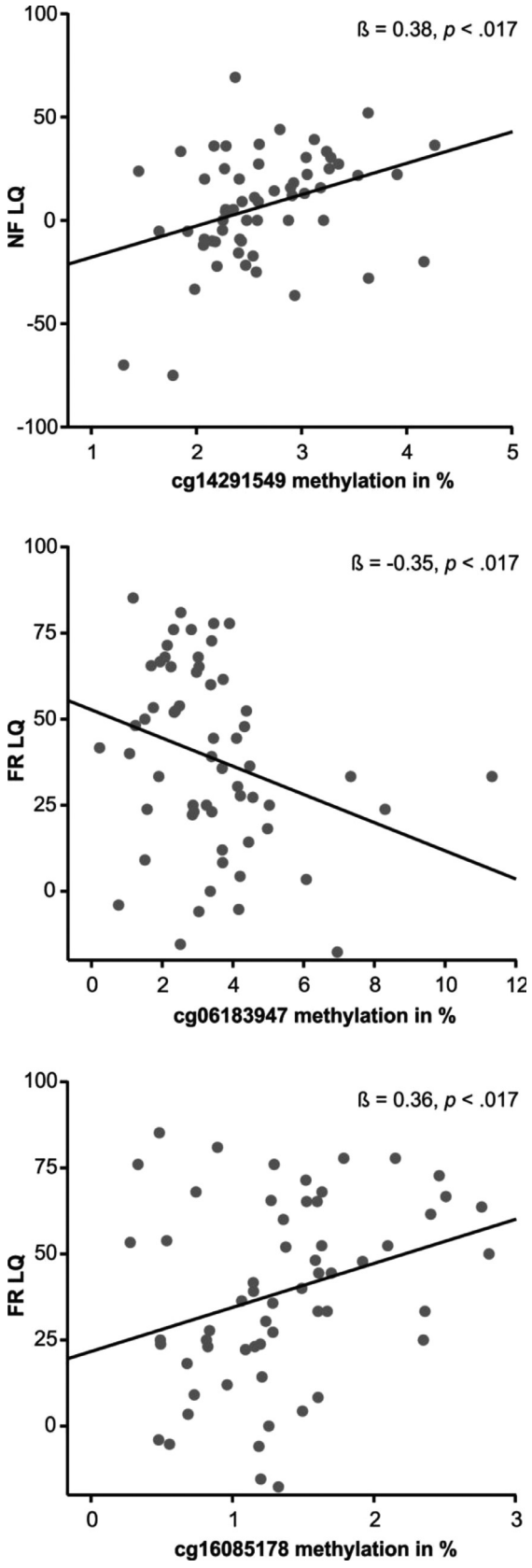

Fig. 3. Scatterplots of *AHI1* DNA methylation and corresponding total dichotic listening LQs A) in the NF condition as well as B) and C) in the FR condition.

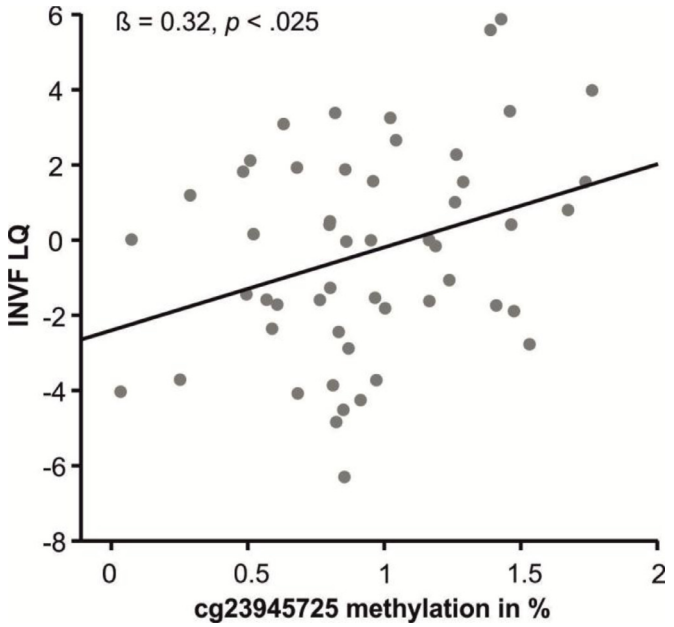

Fig. 4. Scatterplot of *AHI1* DNA methylation and INVF asymmetry. DNA methylation at cg23945725 shows a positive association with INVF LQ.

significance (cg23945725: ß = 0.32, $p < .025$, see Fig. 4). The regression did not reach significance for ODI LQ ($p > .025$).

IMAGE-CpG provided no correlation data for cg23945725.

3.4. Microstructural planum temporale asymmetry and schizotypy

Microstructural *planum temporale* asymmetry was not significantly correlated with schizotypy (INVF LQ: $r = -0.01$, $p = .946$; ODI LQ: $r = 0.14$, $p = .322$).

3.5. Microstructural planum temporale asymmetry and language lateralization

Microstructural *planum temporale* asymmetry was not significantly correlated with language lateralization in the NF (INVF LQ: $r = -0.16$, $p = .251$; ODI LQ: $r = 0.01$, $p = .935$) or FL conditions (INVF LQ: $r = 0.19$, $p = .190$; ODI LQ: $r = –0.03$, $p = .828$). However, INVF LQ showed a significant negative correlation with FR LQ ($r = –0.46$, $p < .00625$, see Fig. 5). ODI LQ was not significantly correlated with FR LQ ($r = 0.04$, $p = .776$).

4. Discussion

This study aimed at investigating associations between DNA methylation in promoter regions of genes involved in cilia function and psychiatric disorders with schizotypy, functional and microstructural hemispheric asymmetries.

4.1. DNA methylation in cilia genes and schizotypy

DNA methylation in the *AHI1* promoter region significantly predicted schizotypal personality. Genetic variation in *AHI1* has been reported to affect schizophrenia susceptibility (Ingason et al., 2010) and response to antipsychotic treatment (Porcelli et al., 2015). *Ahi1* knockdown in zebrafish induces ciliopathies and visceral asymmetry defects (Simms et al., 2012). In mice, *Ahi1* mRNA is highly expressed in cerebellar (Doering et al., 2008) and cortical neurons whose axons cross the midline (Ferland et al., 2004), in line with a role in the ontogenesis of hemispheric asymmetries. Murine Ahi1 maintains tyrosine kinase receptor B (TrkB), a neurotrophic factor receptor (Sheng et al., 2008)

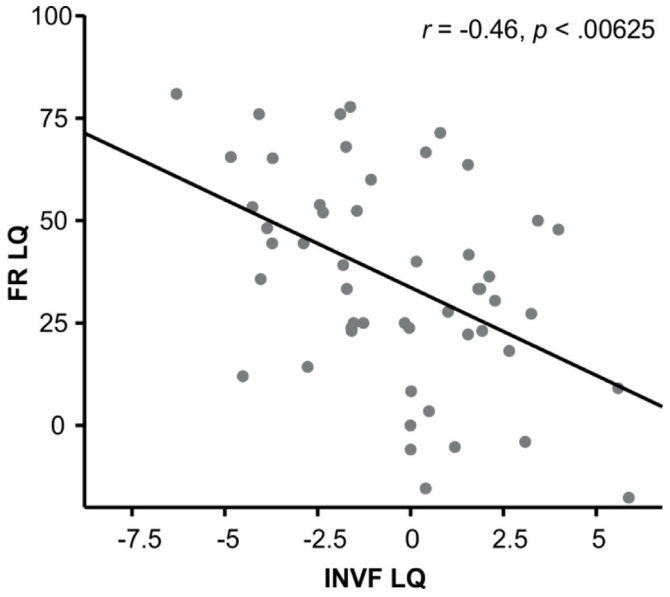

Fig. 5. Scatterplot of INVF LQ and forced-right (FR) LQ. This suggests that more leftward INVF asymmetry is associated with a more pronounced right ear advantage (left hemisphere dominance).

that has been associated with the ontogenesis of visual asymmetry in pigeons (Manns et al., 2005). TrkB is activated by brain-derived neurotrophic factor (BDNF) (Sheng et al., 2008). Serum BDNF is reduced in schizophrenia patients compared to controls (Zhang et al., 2016). Moreover, ocular BDNF injections in pigeons increase contralateral retinal cell sizes and induce visuomotor asymmetries (Manns et al., 2008). Thus, an effect of DNA methylation in the *AHI1* promoter region on schizotypal personality scores in healthy adults raises the question of whether an association might also be found with functional hemispheric asymmetry.

4.2. AHI1 DNA methylation and language lateralization

DNA methylation in the *AHI1* promoter region predicted language lateralization in the NF condition and its attentional modulation in the FR condition. Previously, we found associations of DNA methylation in the *KIAA0319* promoter region with the FL and FR condition (Schmitz et al., 2018b). Interestingly, *KIAA0319* is co-expressed in human cilia (Ivliev et al., 2012) and KIAA0319 contains polycystic kidney disease (PKD) domains that are involved in ciliopathies (Grimes et al., 2016). Thus, the present study provides additional support for a role of DNA methylation in promoter regions of genes involved in visceral asymmetry development in language lateralization. Moreover, our findings are in line with a shared molecular basis of schizotypy and functional hemispheric asymmetries that is based on cilia function (Trulioff et al., 2017).

4.3. AHI1 DNA methylation and microstructural asymmetry of the planum temporale

The left hemisphere dominance for speech perception is reflected in a faster N1 ERP component (Grossi et al., 2010) and it was proposed that this enhanced temporal resolution is based on microstructural properties of the *planum temporale* (Galuske et al., 2000). The left *planum temporale* is characterized by higher INVF and ODI than its right-hemispheric counterpart. The timing of the left-hemispheric N1 component was significantly predicted by left-hemispheric *planum temporale* INVF, but not by macrostructural properties such as volume or thickness (Ocklenburg et al., 2018a). Here, INVF LQ was not significantly different from zero, while ODI LQ was significantly negative, indicating stronger left- than right-hemispheric ODI. DNA methylation in the *AHI1* promoter region significantly predicted INVF asymmetry, with cg23945725 DNA methylation being positively associated with INVF LQ. This is in line with microstructural properties of the *planum temporale* connecting language lateralization and schizotypy.

4.4. Microstructural asymmetry of the planum temporale and schizotypy

Thus, we tested whether *planum temporale* INVF asymmetry is also related to schizotypy and language lateralization. In contrast to our hypothesis, there was no association between INVF or ODI asymmetry and schizotypal personality scores. However, previous research suggests that the molecular factors modulating schizophrenia also modulate *planum temporale* asymmetry and language lateralization. Contrary to controls, schizophrenia patients showed reduced macrostructural *planum temporale* asymmetry and reduced leftward asymmetry in activation during speech perception. Interestingly, non-affected relatives also showed reduced structural and functional asymmetry (Oertel et al., 2010). This association, however, has only been investigated for macrostructural *planum temporale* properties, although *post mortem* studies also argue for atypical laterality in microstructural properties in schizophrenia (Chance, 2014).

4.5. Microstructural asymmetry of the planum temporale and language lateralization

Planum temporale INVF asymmetry was significantly correlated with attentional modulation of language lateralization in the FR condition. The negative correlation between phenotypes was in line with our hypothesis, as it suggests that more leftward INVF asymmetry is associated with a more pronounced right ear advantage (left hemisphere dominance). The fact that the association was only found for the FR, but not for the NF condition is in contrast to previous findings showing an association between INVF asymmetry in *planum temporale* and N1 latency in a passive dichotic listening task (Ocklenburg et al., 2018a). However, participants did not indicate which stimulus they heard, so it is unclear to what extent electrophysiological data and behavioral data in the *iDichotic* app are reflecting the same neuronal mechanisms. Language lateralization is a multidimensional construct that can be measured in terms of perception (as in the *iDichotic* app) vs. production (i.e. based on fTCD) or in terms of performance (*iDichotic*) vs. activation (fMRI) (Ocklenburg et al., 2014). Moreover, the *iDichotic* app measures language lateralization on a continuum of cognitive demand that ranges from low demand in the FR condition (as bottom up and top down instruction are congruent) via intermediate demand in the NF condition to high demand in the FL condition (Kompus et al., 2012). Our findings indicate that microstructural asymmetry in the *planum temporale* is associated with language lateralization when cognitive demand is rather low.

4.6. Limitations

Although the current study provides interesting results regarding molecular factors underlying the association between schizotypy, hemispheric and visceral asymmetry, several limitations apply.

The first limitation is the use of peripheral tissue to investigate neurocognitive phenotypes. The IMAGE-CpG tool revealed a trend towards significance only for cg20128181 in the *AHI1* promoter region, hinting towards similar DNA methylation levels in brain tissue compared to buccal cells. While this finding strengthens the association between DNA methylation in the *AHI1* promoter region and schizotypy scores, either there was no data available for the other CpG sites of interest or DNA methylation was not correlated between tissues. Moreover, it must be mentioned that the brain tissue used for determining the buccal-brain correlation in Braun et al. (2019) was inconsistent between individuals. While in most patients, temporal and

hippocampal tissue was removed, some of the tissue samples include frontal or occipital areas. This makes it impossible to directly infer DNA methylation in the *planum temporale* in our sample from buccal cell DNA methylation. Another possible problem might be that DNA methylation could be altered in pathological, epileptogenic tissue compared to healthy tissue. However, two studies investigated epigenome-wide DNA methylation in temporal lobe tissue from epilepsy patients and histologically normal tissue from autopsies. Only a small number of genes showed DNA methylation patterns that were specific to epilepsy patients (Miller-Delaney et al., 2015; Wang et al., 2016). Thus, despite the use of pathological tissue, DNA methylation at most loci should not show epilepsy-specific patterns.

Second, in this study, we specifically focused on CpG methylation that is independent of genetic variation to explore whether this mechanism might be involved in schizotypy and microstructural asymmetry. However, the investigated phenotypes are of immense complexity and associations can neither be explained by one single molecular mechanism such as DNA methylation nor be found within one gene region (i.e. the *AHI1* promoter region). Besides (poly-) genetic variation, gene-environment interactions (Braff and Tamminga, 2017) and/or other epigenetic modifications such as cytosine methylation outside of the CpG context (Varley et al., 2013) add complexity to resolving the molecular basis of schizotypy and hemispheric asymmetries, making it difficult to choose an appropriate study design to cover all potential molecular mechanisms. Due to the available sample size, we chose to focus on DNA methylation independent of genetic variation. One strategy developed in molecular psychiatric research is to break down psychiatric diagnoses into heritable biomarkers called endophenotypes to enable the identification of associated genetic markers (Gottesman and Gould, 2003). Moreover, future imaging studies will expand from candidate-gene studies to (epi-) genome-wide studies, providing opportunities for both validation of candidate gene regions and discovery of new associated gene regions (Arslan, 2018).

Third, some statistical considerations need to be kept in mind. It has been argued that particularly high correlations between personality measures and imaging parameters are likely to be false positives as the strength of correlation between two indices is restricted by their respective reliabilities (Vul et al., 2009). However, while high test-retest reliabilities have been reported for the SPQ (Raine, 1991) and the *iDichotic* app (Bless et al., 2013), the reliability of NODDI measures has not yet been determined. Moreover, it has to be noted that our sample size was comparatively small and better powered studies are necessary to reach conclusive results (Ioannidis, 2005).

4.7. Outlook and conclusion

Overall, DNA methylation in the *AHI1* promoter region is a promising molecular factor that might underlie the association between schizotypy, hemispheric and visceral asymmetry. While in this study, schizotypal personality scores were low, future studies should replicate these associations in larger samples to better assess specific subscores of schizotypal personality. The association between *AHI1* DNA methylation and schizotypy was mainly driven by the subscales IR and S and it might be that associations with laterality might only be evident in subcomponents as well. This observation supports a symptom-based approach for the relation between schizophrenia and hemispheric asymmetry (Ocklenburg et al., 2015). For example, there is evidence for atypical language lateralization in schizophrenia that depends on the extent of auditory hallucinations (Ocklenburg et al., 2013c). Moreover, other asymmetry phenotypes could be taken into account, as it has been shown that mixed-footedness is more closely related to schizotypy than mixed-handedness (Tran et al., 2015).

In conclusion, DNA methylation in the *AHI1* promoter region (obtained from peripheral cells) predicts schizotypy, language lateralization and microstructural asymmetry in the *planum temporale* in the current study. However, as mentioned above, future research remains to elucidate if interindividual variation in DNA methylation in the *AHI1* promoter region reflects brain DNA methylation. Our results are in line with the suggestion of a shared molecular basis of schizotypy and functional hemispheric asymmetries that is based on cilia function.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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