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PLP1 Gene Variation Modulates Leftward and Rightward Functional Hemispheric Asymmetries

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Abstract

Molecular neurobiological factors determining corpus callosum physiology and anatomy have been suggested to be one of the major factors determining functional hemispheric asymmetries. Recently, it was shown that allelic variations in two myelin-related genes, the proteolipid protein 1 gene *PLP1* and the contactin 1 gene *CNTN1*, are associated with differences in inter-hemispheric integration. Here, we investigated whether three single nucleotide polymorphisms that were associated with inter-hemispheric integration via the corpus callosum in a previous study also are relevant for functional hemispheric asymmetries. To this end, we tested more than 900 healthy adults with the forced attention dichotic listening task, a paradigm to assess language lateralization and its modulation by cognitive control processes. Moreover, we used the line bisection task, a paradigm to assess functional hemispheric asymmetries in spatial attention. We found that a polymorphism in *PLP1*, but not *CNTN1*, was associated with performance differences in both tasks. Both functional hemispheric asymmetries and their modulation by cognitive control processes were affected. These findings suggest that both left and right hemisphere dominant cognitive functions can be modulated by allelic variation in genes affecting corpus callosum structure. Moreover, higher order cognitive processes may be relevant parameters when investigating the molecular basis of hemispheric asymmetries.

Keywords Corpus callosum · Myelin · Functional hemispheric asymmetries · Dichotic listening · Line bisection · Molecular genetics

Introduction

For many cognitive functions, the human brain shows functional hemispheric asymmetries, e.g., performance differences between the left and the right hemisphere [1, 2]. Asymmetrically organized cognitive systems for example include language [3], face processing [4], emotions [5], visuo-spatial attention [6], and self-awareness [7].

The neurophysiology underlying the emergence of such a division of function between the left and the right side of the brain is still not well understood. One idea that has been discussed by several authors is that the strength of hemispheric asymmetries critically depends on the functioning of the corpus callosum, the major commissure connecting the two hemispheres of the cerebral cortex [8]. Most callosal axons are glutamatergic and therefore excitatory, but since they connect to inhibitory interneurons, callosal information transfer can also be inhibitory [9]. Therefore, both excitatory and inhibitory models have been proposed to

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explain the role of the corpus callosum for the emergence of hemispheric asymmetries. In principle, the excitatory model assumes that less efficient interhemispheric transfer would lead to stronger hemispheric asymmetries, since time-sensitive processes would be more likely to be performed by fast neural networks in one hemisphere, if transmission over the corpus callosum is slow [10]. In contrast, the inhibitory model assumes that the dominant hemisphere inhibits the function of the subdominant hemisphere via the corpus callosum [11]. Therefore, less efficient interhemispheric transfer via the corpus callosum would lead to reduced hemispheric asymmetries. While the two models seem to contradict each other, several authors concluded that the corpus callosum is likely to serve both excitatory and inhibitory influences on the contralateral hemisphere [9, 12]. Thus, both models could be correct, only for different callosal fiber types or subregions.

The speed of interhemispheric information transfer for a specific callosal axon is largely determined by two factors: First, axon conduction speed is determined by the diameter of the axon, with thicker axons having a higher information transfer velocity [13]. Second, axon myelination enhances the speed of neuronal information transfer [14]. Due to this critical role of myelin for the speed of interhemispheric transfer of information, we have recently suggested that genes involved in oligodendrocyte development and survival, as well as in myelin sheath formation and the axon ensheathment process, constitute interesting candidate genes for investigating the molecular basis of inter-individual differences in interhemispheric integration [15]. To test this assumption, we previously genotyped a cohort of 453 healthy adults for 18 single nucleotide polymorphisms (SNPs) in six myelin-related candidate genes (*PLP1*, *GPM6A*, *MOG*, *MBP*, *CNTN1*, and *MOBP*) and tested the participants with the Banich-Belger Task [16], a widely used paradigm to assess interhemispheric integration. We found that two SNPs in the proteolipid protein 1 gene *PLP1* and one SNP in the contactin 1 gene *CNTN1* correlated with the extent to which individual performance in the Banich-Belger task was enhanced by interhemispheric integration. Based on these results, we concluded that variation in myelin genes indeed plays a role for inter-individual differences in interhemispheric integration. The present study was aimed at investigating, whether the three SNPs we identified in our previous study (*CNTN1* rs1056019, *PLP1* rs1126707, and *PLP1* rs521895) also play a role for functional hemispheric asymmetries, as would be predicted by models that assume that the corpus callosum influences hemispheric asymmetries. To this end, we tested a new independent cohort of 970 individuals with two behavioral tasks to assess functional hemispheric asymmetries. One task was used to assess language lateralization, a left hemisphere dominant function, and another task was used to assess laterality of visuo-spatial attention, a right hemisphere dominant function.

In order to assess language lateralization, we used the forced attention dichotic listening task [17, 18], implemented in the iDichotic smartphone app [19–22]. This task consists of three conditions: The first condition is the so-called non-forced (NF) condition. This condition is identical to the classic consonant-vowel dichotic listening task [23], the most widely used behavioral task to determine individual language lateralization. In this task, participants wear headphones and simultaneously hear two different syllables, e.g., BA and GA, in both ears. They are instructed to report the syllable which they heard best. Typically, most participants report more syllables that had been presented to the right ear. As information presented to the right ear is mostly processed by the left hemisphere, this so-called right-ear advantage (REA) has been thought to reflect left hemispheric dominance for auditory processing of speech stimuli [24]. In addition, the forced attention dichotic listening task compromised two so-called "forced" conditions. In the forced-right (FR) condition, participants are instructed to concentrate only on the syllables presented to the right ear. In contrast, in the forced-left (FL) condition, they are instructed to attend only to the syllables presented to the left ear. Typically, the REA observed in the NF condition is even stronger in the FR condition, but reduced in the FL condition [25, 26]. To include the FR and FL conditions is important, as they allow assessing how lateralized bottom-up driven perceptual processing is modulated by top-down cognitive control processes [27–29]. We have particularly chosen the dichotic listening task to assess language lateralization in relation to variation in *PLP1* and *CNTN1*, since two recent review articles suggested a strong link between corpus callosum function and dichotic listening performance, notably when cognitive control processes are involved, e.g., mediating attention to one ear in the forced conditions [30, 31].

In order to assess visuo-spatial attention, we used the classic line bisection task [32]. In this task, participants have to mark the center of several horizontal lines printed on a sheet of paper. Typically, neurologically healthy individuals show a phenomenon called pseudoneglect in this task, e.g., they bisect the line to the left of its veridical center [33]. Pseudoneglect is thought to reflect a dominance of the right hemisphere for visuo-spatial attention [34]. Like performance in the forced attention dichotic listening task, performance in the line bisection task can be modulated by directing attention towards one side. This can either be done by using the left or the right hand to perform the bisection or by varying the position of the lines in relation to the center of the sheet. Jewell and McCourt [32] reported that while line bisection performed with both hands on average yields a leftward bisection bias, there is a relative bias in the direction of the hand that is used. Similarly, there is also a relative bias in the direction of stimulus location. Thus, a line that is located on the left side of the sheet will elicit stronger pseudoneglect than a central line. In contrast, a line that is located on the right side of the sheet will elicit weaker pseudoneglect than a central line. Comparable to the forced attention dichotic listening task, performance in the line

bisection task is affected by corpus callosum structure, as patients in which the whole corpus callosum or its posterior part has been sectioned show massively altered performance in this task [35]. Moreover, developmental changes in line bisection performance have been suggested to reflect callosal maturation [36, 37].

As performance in both the forced attention dichotic listening task and the line bisection task has been suggested to be influenced by inter-individual variability in corpus callosum structure, we hypothesize that genetic variability in *CNTN1* and *PLP1* should affect performance in these tasks.

Materials and Methods

Cohort

Overall, we tested 970 neurologically healthy adults (662 females and 308 males). Participants had a mean age of 24.27 years (range, 18 to 66 years) and were mostly university students. Participants were genetically unrelated to each other, as assessed by self-report. The majority of participants were German. The average handedness lateralization quotient (LQ) as determined with the Edinburgh Handedness inventory [38] was 71.75 (range, − 100 to 100). Participants were considered left-handed if their LQ was negative and right-handed if their LQ was positive. There were no participants with an LQ of exactly zero. There were 8.4% left-handers (negative LQ) and 91.6% right-handers (positive LQ) in the sample. There were no left-handers that had been forced to write with their right hand in the cohort. Prior to testing, hearing capabilities were tested with the hearing test included in the iDichotic app [19, 21]. Only participants with normal hearing capabilities and no pronounced asymmetries in hearing capabilities were included in the cohort. Both left and right handers were included in the cohort. The study was approved by the ethics committee of the medical faculty, Ruhr-University Bochum. All participants gave written informed consent and were treated in accordance with the declaration of Helsinki.

Genotyping

From each participant, oral mucosa samples were collected using buccal swabs. Exfoliated cells were used for DNA isolation, which was performed using the QIAamp DNA mini kit (Qiagen GmbH, Hilden, Germany). SNP genotyping was performed using polymerase chain reaction (PCR) followed by restriction length polymorphism. PCR-RFLP methodology can be found in [39]. Further details and primer sequences are available upon request. Based on the associations reported in our previous study on myelin genes and interhemispheric integration, we focused on three different SNPs: one in the *CNTN1* gene (NM_001843): rs1056019, a synonymous exchange N472N located in exon 11 and two in the *PLP1* gene (NM_001128834): rs1126707, a synonymous exchange D203D in exon 11, and the variation rs521895 located in intron 3 [15]. In our previous study, these SNPs revealed statistically significant effects in interhemispheric integration via the corpus callosum. Therefore, they were chosen for further analysis in a different cohort analyzing functional hemispheric asymmetries applying the following tasks.

Forced Attention Dichotic Listening Task

We used the iDichotic app for iOS, freely available in the Apple app store, to test participants with forced attention dichotic listening task [19, 21]. We have used this app previously in a family study on the heritability of language lateralization and cognitive control [20]. Participants were tested in a quiet room using an Apple iPod touch (Apple Inc., Cupertino, CA) and over-the-ear headphones outfitted with disposable hygienic sleeves. Stimuli consisted of the six classic consonant-vowel syllables with durations between 400 and 500 ms (Ba, Da, Ga, Ka, Pa, Ta). They were adapted from the standard Bergen dichotic listening paradigm [40]. Stimuli were always presented simultaneously in pairs, one to each ear. This resulted in six homonym stimulus pairs, in which the same stimulus was presented to both ears (e.g., Ta-Ta) and 30 dichotic stimulus pairs, in which two different stimuli were presented to the two ears (e.g., Ga-Ga). The total number of stimulus pairs was 36. The onsets of the initial stop-consonants were temporally aligned to each other within stimulus pairs. Since testing took place in Germany, we used the German language version of the iDichotic app, in which the syllables were spoken by a male German speaker with constant intensity and intonation. Between two stimulus pairs, there was an inter-stimulus interval of 4 s.

The task had three different experimental conditions. In the NF condition , participants were instructed to report the syllable heard most clearly. In the FR condition, participants were instructed to only attend to the right ear and report the syllable they heard on that ear. In the FL condition, participants were instructed to only attend to the left ear and report the syllable they heard on that ear. Participants had to react by touching one out of six fields showing the six syllables on the touchscreen of the iPod Touch. The order in which the fields with six syllables appeared on the reaction screen was randomized, for every participant and every condition.

Line Bisection Task

In order to assess functional hemispheric asymmetries in visuo-spatial attention, a visual line bisection task was conducted in a subsample of 518 participants [32]. In this task, a sheet of paper (size, 210 mm × 297 mm) containing 17 horizontal black lines was positioned on a table in front of the

participant's midline [37, 41]. Seven lines were positioned in the middle of the sheet, five were positioned on the right side of the sheet, and five were positioned on the left side of the sheet. Participants were handed a black pencil and asked to bisect each of the 17 lines into two equal parts. The line bisection task was conducted once with the right and once with the left hand, in randomized order. Thus, overall, there were six different conditions in this task (left, right, and central lines bisected with either the left or the right hand).

Statistical Analyses

The data were analyzed parametrically with ANOVAs. For the forced attention dichotic listening task, the data for the three SNPs were analyzed with 3 × 2 × 3 (*CNTN1*) or 5 (*PLP1*) repeated measures ANOVAs with the within-subjects factor condition (NF, FR, FL) and ear (left ear, right ear) as within-subjects factors and the *CNTN1 (CC*, *CT*, *TT)* or *PLP1* genotype (rs1126707: C, T, CC, CT, TT; rs521895: A, G, AA, AG, GG) as between-subjects factors. For the line bisection task, the data for the three SNPs were analyzed with 3 × 2 × 3 (*CNTN1*) or 5 (*PLP1*) repeated measures ANOVAs with the within-subjects factor line position (central, left right) and hand (left hand, right hand) as within-subjects factors and the *CNTN1* or *PLP1* genotype as between-subjects factors. For all significant key effects, it is indicated whether they would survive Bonferroni correction for the number of investigated SNPs. Partial Eta Squared is given as a measure of effect size. All post-hoc tests were corrected for multiple comparisons using Bonferroni correction.

Results

Genotype Distributions

For *CNTN1* rs1056019, 15.7% of the participants showed the homozygous CC genotype, 41.8% were typed heterozygous CT and 41.4% homozygous TT. In 11 participants (1.1%), the genotype could not be determined due to technical issues. The MAF reported for the *CNTN1* rs1056019 SNP in dbSNP (https://www.ncbi.nlm.nih.gov/projects/SNP/) is between 0.37 and 0.43. In line with this, we found a MAF of 0.37 for this SNP in our cohort (with C being the minor allele).

Genotyping *PLP1* rs1126707 revealed five different genotypes, as this gene is located on the X chromosome (C and T for male individuals and CC, CT, and TT for female individuals). Therefore, we calculated genotype percentages separately for male and female participants. For male participants, 26% showed the C genotype and 72% showed the T genotype. For female participants, 9% showed the CC genotype, 40% the CT genotype, and 50% the TT genotype. In seven participants, the genotype could not be determined due to technical issues. The MAF reported for the *PLP1* rs1126707 SNP in dbSNP (https://www.ncbi.nlm.nih.gov/projects/SNP/) is between 0.20 and 0.28. For male participants, the MAF in our sample was 0.26, and for female participants, it was 0.29, resulting in a combined MAF of 0.275. Thus, the MAF observed in our sample is in line with what would be expected in the population.

For *PLP1* rs521895, there were also five different genotypes (A and G for male individuals and AA, AG, and GG for female individuals). Therefore, we calculated genotype percentages separately for male and female participants. For male participants, 30% showed the A genotype and 66% the G genotype. For female participants, 10% showed the AA genotype, 43% showed the AG genotype, and 47% showed the GG genotype. In 11 participants, the genotype could not be determined due to technical issues. The MAF reported for the *PLP1* rs521895 SNP in dbSNP (https://www.ncbi.nlm.nih.gov/projects/SNP/) is 0.38. For male participants, the MAF in our sample was 0.30, and for female participants, it was 0.42, resulting in a combined MAF of 0.36. Thus, the MAF observed in our sample is in line with what would be expected in the population.

Forced Attention Dichotic Listening Task

We first analyzed the forced attention dichotic listening task without integrating genotypes in the analysis in order to test, whether our results in general could replicate the typical findings for this task. To this end, we calculated a 3 × 2 repeated measures ANOVA with the within-subjects factor condition (NF, FR, FL) and ear (right ear, left ear). Both, the main effects condition ($F_{(2,\ 968)} = 160.91$; $p < 0.001$; partial $\eta^2 = 0.14$) and ear ($F_{(1,\ 969)} = 293.08$; $p < 0.001$; partial $\eta^2 = 0.23$) as well as the interaction condition × ear ($F_{(2,\ 968)} = 773.30$; $p < 0.001$; partial $\eta^2 = 0.44$) reached significance. Bonferroni-corrected post-hoc tests revealed a significant REA in the NF condition ($p < 0.001$) that was even stronger in the FR condition ($p < 0.001$) (see Fig. 1 for descriptive statistics). In the FL condition, there was a significant left ear advantage ($p < 0.001$).

In order to investigate whether *CNTN1* rs1056019 genotypes were related to performance in the forced attention dichotic listening paradigm, we recalculated the analysis of the dichotic listening data with *CNTN1* rs1056019 genotypes as an additional between-subjects factor. However, neither the main effect *CNTN1* rs1056019 genotype nor any interactions with this factor reached significance (all p's > 0.29).

Applying the same analysis to the *PLP1* rs1126707 SNP (see Fig. 2 for descriptive statistics) revealed no significance for the main effect of *PLP1* rs1126707 genotype ($F_{(4,\ 956)} = 0.55$; $p = 0.70$). However, the genotype × ear interaction approached significance ($F_{(4,\ 956)} = 2.18$; $p = 0.07$). Interestingly, the genotype × ear × condition interaction also reached significance ($F_{(4,\ 956)} = 2.79$; $p = 0.01$; partial $\eta^2 =$

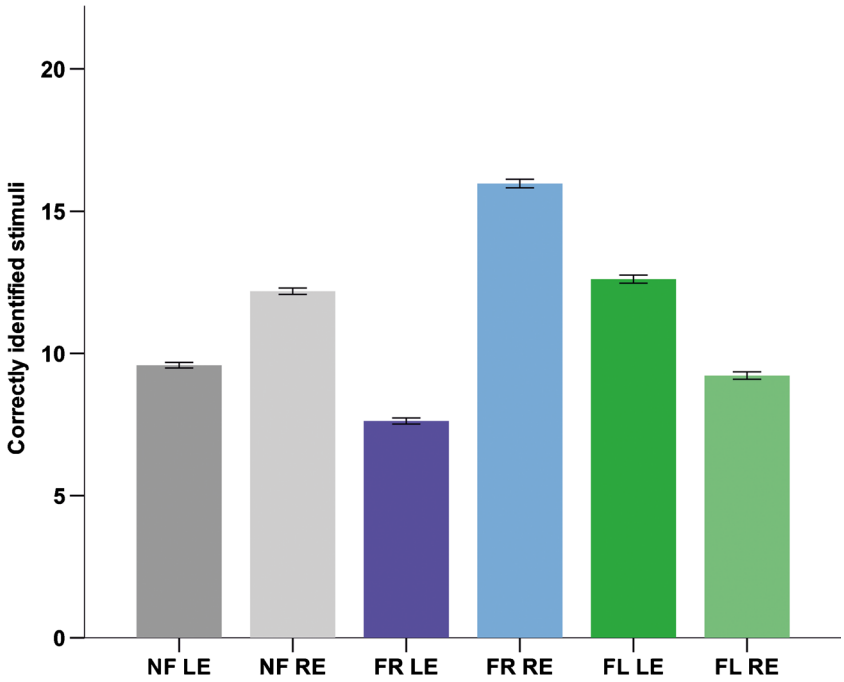

Fig. 1 Correctly identified stimuli in the forced attention dichotic listening paradigm for the left ear (LE) and the right ear (RE) in the non-forced (NF), forced-right (FR), and forced-left (FL) condition. Error bars show standard error

0.012). With a p value of $p = 0.01$, this effect would survive a correction of the statistical threshold to reach significance by the number of investigated SNPs (Bonferroni-corrected significance threshold: $p = 0.017$). To further investigate this effect, we performed Bonferroni-corrected post-hoc tests comparing left- and right-ear performance for all five genotypes in all three conditions (corrected significance threshold: $p = 0.0033$). Overall, all but two post-hoc tests reached significance ($p < 0.001$), indicating significant hemispheric asymmetries for all three conditions of the forced attention dichotic listening task for most genotypes. However, for male participants with the C genotype, this comparison failed to reach significance in the FL condition ($p = 0.025$), and for female participants with the CC genotype, this comparison failed to reach significance for the NF condition ($p = 0.11$).

For the *PLP1* rs521895 (see Fig. 3 for descriptive statistics), both the main effect of *PLP1* rs521895 genotype ($F_{(4, 952)} = 0.58$; $p = 0.68$) and the genotype × ear interaction failed

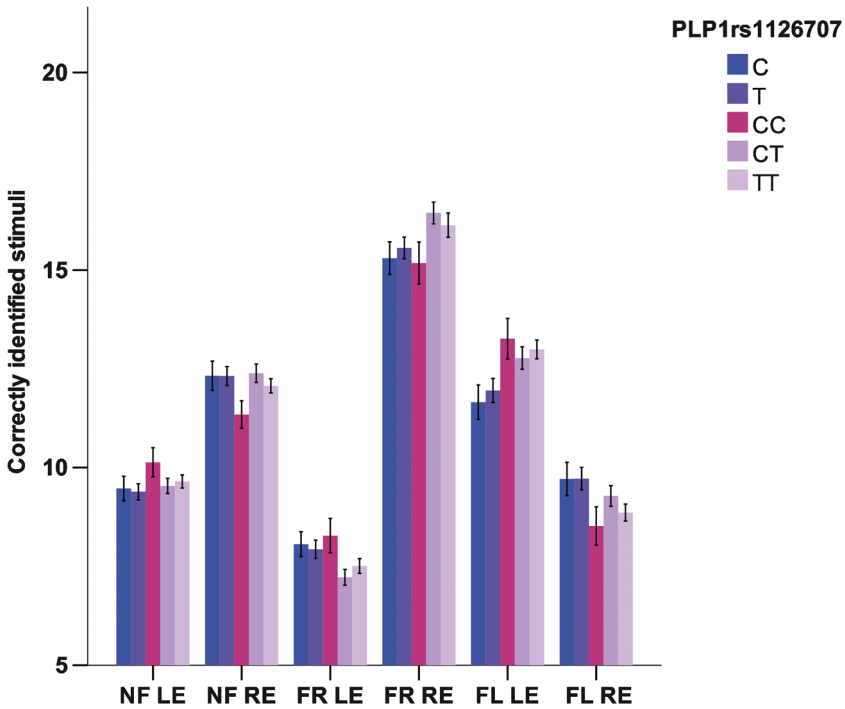

Fig. 2 Correctly identified stimuli in the forced attention dichotic listening paradigm for the left ear (LE) and the right ear (RE) in the non-forced (NF), forced-right (FR), and forced-left (FL) condition in relation to *PLP1* rs1126707 genotype. Error bars show standard error

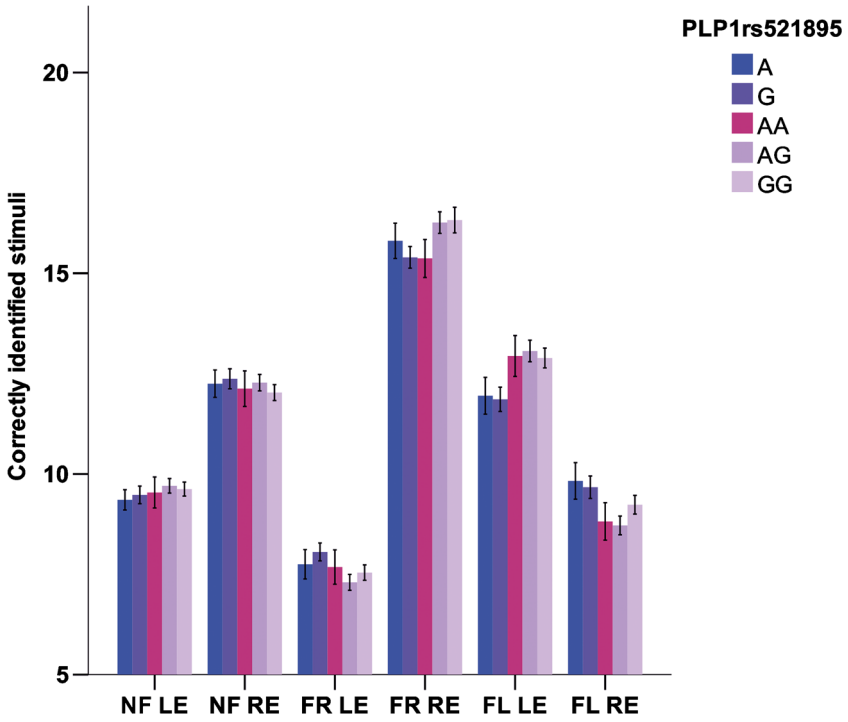

Fig. 3 Correctly identified stimuli in the forced attention dichotic listening paradigm for the left ear (LE) and the right ear (RE) in the non-forced (NF), forced-right (FR), and forced-left (FL) condition in relation to *PLP1* rs521895 genotype. Error bars show standard error

to reach significance ($F_{(4, 956)} = 0.48$; $p = 0.75$). Interestingly, the genotype × ear × condition interaction reached significance ($F_{(4, 956)} = 3.16$; $p = 0.004$; partial $\eta^2 = 0.013$). With a p value of $p = 0.004$, this effect would remain significant after a correction of the statistical threshold to reach significance by the number of investigated SNPs (Bonferroni-corrected significance threshold: $p = 0.017$). To further investigate this effect, we performed Bonferroni-corrected post-hoc tests comparing left- and right-ear performance for all five genotypes in all three conditions (corrected significance threshold: $p = 0.0033$). Overall, all but one post-hoc tests reached significance ($p < 0.001$), indicating significant hemispheric asymmetries for all three conditions of the forced attention dichotic listening task for all but one genotype. However, for male participants with the A genotype, this comparison failed to reach significance in the FL condition ($p = 0.008$).

Line Bisection Task

As mentioned above, the line bisection task was conducted in a subsample of 518 participants. We first analyzed the line bisection without integrating genotypes in the analysis in order to test, whether our results in general could replicate the typical findings for this task. On average, participants showed significant pseudoneglect (0.79% leftward bias, $t_{(517)} = -7.25$; $p < 0.001$). To investigate how the different conditions affected this bias, we calculated a 3 × 2 repeated measures ANOVA with the within-subjects factor line position (central, right, left) and hand used to bisect the line (right hand, left hand). Both, the main effects line position ($F_{(2, 516)} = 400.19$; $p < 0.001$; partial $\eta^2 = 0.44$) and hand used to bisect the line ($F_{(1, 517)} = 104.02$; $p < 0.001$; partial $\eta^2 = 0.17$) as well as the interaction line position × hand used to bisect the line ($F_{(2, 516)} = 34.64$; $p < 0.001$; partial $\eta^2 = 0.06$) reached significance (see Fig. 4 for descriptive statistics). To further investigate this effect, we calculated Bonferroni-corrected one-sample t tests for each of the six different conditions to test for the existence of pseudoneglect. For both left hand and right hand use, significant pseudoneglect was found for central line positioning and leftward line positioning (all p's < 0.011). In contrast to central and leftward line position, a rightward bias was found for rightward line position (both p's $p < 0.001$). We then calculated Bonferroni-corrected post-hoc tests to see whether the used hand also affected the attentional bias. Indeed, there was a significantly stronger pseudoneglect for central and left line position, when the left hand was used then when the right hand was used (both p's < 0.001). In contrast, the rightward bias for rightward line position was reduced when the left hand was used compared to the use of the right hand ($p < 0.001$).

In order to investigate, whether the *CNTN1* rs1056019 SNP was related to performance in the line bisection task, we recalculated the analysis of the line bisection data with *CNTN1* rs1056019 genotype as an additional between-subjects factor. However, neither the main effect *CNTN1* rs1056019 genotype nor any interactions with this factor reached significance (all p's > 0.43).

Recalculating the analysis of the line bisection data with *PLP1* rs1126707 genotype as an additional between-subjects factor (see Fig. 5 for descriptive statistics) reached significance

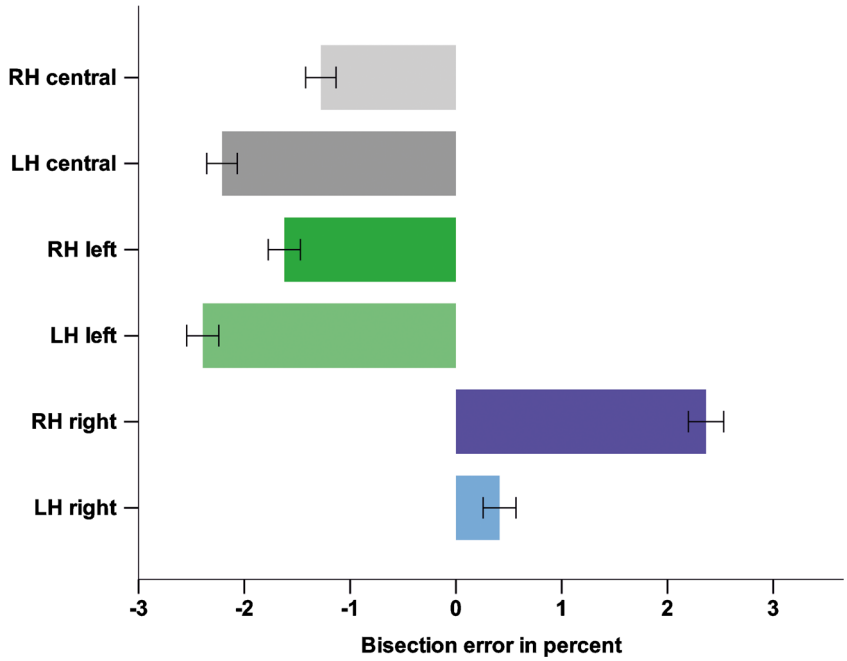

Fig. 4 Bisection error in percent for central, leftward, and rightward lines in the line bisection task. Line bisection was performed with either the right hand (RH) or the left hand (LH)

for the interaction genotype × line position ($F_{(2, 507)} = 3.26$; $p = 0.0027$; partial $\eta^2 = 0.025$). With a p value of $p = 0.0027$, this effect would remain significant after a correction of the statistical threshold to reach significance by the number of investigated SNPs (Bonferroni-corrected significance threshold: $p = 0.017$). To further investigate this effect, we performed Bonferroni-corrected post-hoc tests comparing the three line positions for all five genotypes (corrected significance threshold: $p = 0.0033$). All five genotypes showed a rightward bisection bias for rightward line position that was significantly different from the pseudoneglect observed for central and leftward line positions (all p's < 0.001). However, only the C genotype showed a significant difference between central and leftward line positions ($p < 0.001$), indicating a stronger pseudoneglect for leftward than for central lines. This comparison also showed a nominally significant trend for the CT genotype ($p = 0.021$), which however did not survive correction for multiple comparisons. For the CC genotype, the comparison approached nominal significance ($p = 0.07$). For the T and TT genotypes, the post-hoc tests failed to reach

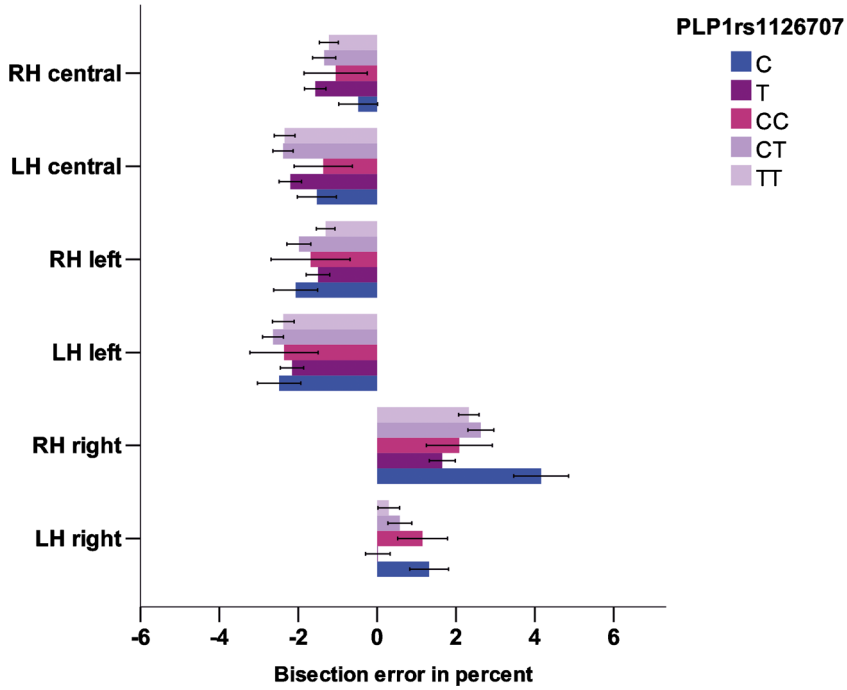

Fig. 5 Bisection error in percent for central, leftward, and rightward lines in the line bisection task in relation to *PLP1* rs1126707 genotype. Line bisection was performed with either the right hand (RH) or the left hand (LH)

significance (all p's > 0.74). The main effect genotype, as well as all other interactions with genotype failed to reach significance (all p's < 0.34).

For the *PLP1* rs521895 SNP, the main effect genotype and all interactions with genotype failed to reach significance (all p's > 0.08).

Discussion

The aim of the present study was to investigate, whether allelic variation in myelin-associated genes might affect leftward as well as rightward functional hemispheric asymmetries. In a previous study, we had shown that three SNPs (*CNTN1* rs1056019, *PLP1* rs1126707, and *PLP1* rs521895) correlated with the extent to which individual performance in the Banich-Belger task was enhanced by interhemispheric integration [15]. Here, we tested whether these SNPs also affected functional hemispheric asymmetries for auditory speech perception in visuo-spatial attention.

The analysis of the behavioral data revealed that the commonly reported findings could be replicated for the two paradigms used. In the forced attention dichotic listening task, we found a right-ear advantage in the NF condition that was enhanced in the FR condition, but reduced in the FL condition. This is in line with what has been reported for the forced attention dichotic listening paradigm in other studies [17, 18, 25]. For the line bisection task, we found significant pseudoneglect for left and central line positions, but a rightward attention bias for right line positions. Moreover, the hand used to bisect the line affected the attentional bias, with left hand use shifting attention to the left. This is in line with the findings of the largest meta-analysis on line bisection [32].

While our previous study showed an association between the *CNTN1* rs1056019 and interhemispheric integration, we did not find any association between in the genotypes of this SNP and functional hemispheric asymmetries. We did, however, identify a significant association between the two tested *PLP1* SNPs and performance in, both the forced attention dichotic listening task and the line bisection task. For the forced attention dichotic listening task, the genotype × ear × condition interaction reached significance for both *PLP1* SNPs.

For *PLP1* rs1126707, we found that the minor C allele was associated with a condition-specific reduction of hemispheric asymmetries. Compared to the other genotypes, male individuals with the C genotype did not show a significant LEA (left ear advantage) in the FL condition. Interestingly, a specific impairment of forced attention dichotic listening performance in the FL condition has also been shown in schizophrenia [40], a disorder that has widely been associated with altered hemispheric asymmetries [42]. Schizophrenia has also been associated with altered *PLP1* gene function. A microarray analysis of postmortem temporal cortex samples from schizophrenic patients revealed a significant decrease of *PLP1* expression compared to brain samples obtained from non-schizophrenic controls [43]. Moreover, a family-based association study in a Chinese sample reported a significant association between genetic variation in the *PLP1* rs475827 SNP and schizophrenia [44]. While there are no direct links between allelic variations in the two SNP's investigated in the present study and schizophrenia, these links indicate that future studies should further investigate the link between *PLP1*, schizophrenia, and altered hemispheric asymmetries. Males with the C genotype showed a specific performance effect in the FL condition, while their performance in the NF condition was unimpaired. This indicates that genetic variation in *PLP1* affects the extent to which cognitive control of attention towards one ear affects lateralization. In comparison to other genotypes, the C group seemed to be less able to focus their attention on the left ear. This relation between genetic variation in *PLP1* and mediating attention to one ear in the FL conditions is in line with the idea that the corpus callosum is particularly important for dichotic listening performance when cognitive control processes are involved [31]. This idea is further supported by the findings for *PLP1* rs521895. Here, also, a specific genotype effect was found for the FL condition, but not the NF condition.

In addition to the finding in C genotype males, female individuals with the CC genotype did not show a significant REA in the NF condition, in contrast to all other genotypes. Thus, this group showed a reduction of hemispheric asymmetries in the NF condition. In Kimura's classic structural model of dichotic listening [45, 46], it is assumed that in the NF condition, both the left and the right auditory cortex receive projections from each ear. The syllable presented to the right ear has preferential access to the language-dominant left hemisphere, while the syllable presented to the left ear is first processed by the right hemisphere and the neural information has to be transferred to the left hemisphere over the corpus callosum. Thus, in this model the corpus callosum would excitatory transport information from the right to the left hemisphere. A reduction of the REA in the CC genotype group would therefore indicate a more efficient corpus callosum in this group, as left ear syllables would reach the left hemisphere faster, leading to a reduction of the REA in the NF condition.

For the line bisection task, we also found an effect of genetic variation in the *PLP1* rs1126707 SNP. As for the forced attention dichotic listening task, male individuals carrying the C allele stood out. They were the only group that showed a significantly stronger pseudoneglect for lines that were positioned on the left side of the paper, as compared to central lines. They also showed the absolutely strongest rightward shift for lines positioned on the right side of the paper. Thus, attentional modulation by line positioning to one side had a

stronger impact on participants with this genotype than on participants with other genotypes.

Our finding that C males and CC females show specific changes in hemispheric asymmetries is in line with the results of our previous study on *PLP1* variation and corpus callosum function [15]. In this study, we had found that males with the C genotype showed a stronger across field advantage in the complex name identify condition of the Banich-Belger task than males with the T genotype [15]. This indicates that under high-task demands, male carriers of the C allele benefit more from interhemispheric integration via the corpus callosum than male carriers of the T allele. CC females had an across field advantage that was comparably large to that of the C males and were also significantly different from male carriers of the T allele. These findings potentially imply that C males and CC female genotypes revealed a higher efficiency in callosal information processing in this study.

Thus, taken together, our results suggest that genetic variation in *PLP1* could affect functional hemispheric asymmetries. *PLP1* is located at Xq22.2 and encodes a transmembrane protein that is one of the major components of myelin [47]. It is also involved in axon-oligodendrocyte interaction and wrapping of the axon [48]. Mutations in *PLP1* have been found to cause Pelizaeus-Merzbacher disease and hereditary spastic paraplegia type 2, two well-characterized types of dysmyelinating leukodystrophies in the central nervous system [49]. In a transgenic mouse model of Pelizaeus-Merzbacher disease, it has been shown that the microstructural integrity of the CC is reduced [50], implying a direct relevance of genetic variation in *PLP1* for CC structure. Thus, it could be conceived that genetic variation in *PLP1* affects functional hemispheric asymmetries by modulating the microstructure of the CC. Altered callosal microstructure could modulate the efficacy of callosal transmission which in turn affects functional hemispheric asymmetries and how they are modulated by cognitive control processes.

Our findings are central for the ongoing discussion about the molecular determinants of functional hemispheric asymmetries by suggesting for the first time that myelin-related genes might represent a potential influence factor. Importantly, we could show that genetic variation in *PLP1* affects both performance in a left-dominant language task and a right-dominant visuo-spatial attention task. Importantly, this implies that myelin-related genes might affect functional hemispheric asymmetries unspecific of the cognitive system that is involved. This is currently not considered in theoretical account of functional hemispheric asymmetries. Further research with other forms of functional hemispheric asymmetries is needed to test this idea. Moreover, our findings also imply the top-down cognitive control processes are a relevant parameter when investigating the molecular basis of functional hemispheric asymmetries, as suggested before [51, 52].

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Compliance with Ethical Standards

Conflicts of Interests The authors declare that they have no conflict of interest.

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