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Myelin Genes and the Corpus Callosum: Proteolipid Protein 1 (*PLP1*) and Contactin 1 (*CNTN1*) Gene Variation Modulates Interhemispheric Integration

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Abstract Interhemispheric communication during demanding cognitive tasks shows pronounced interindividual variation. Differences in interhemispheric transfer time are constituted by the relative composition of slow and fast fibers. The speed of axonal conduction depends on the diameter of the axon and its myelination. To understand the possible genetic impact of myelin genes on performance in the Banich-Belger Task, a widely used paradigm to assess interhemispheric integration, 453 healthy adults were genotyped for 18 single nucleotide polymorphisms (SNPs) in six myelin-related candidate genes. We replicated the typical pattern of results in the Banich-Belger Task, supporting the idea that performance on cognitively demanding tasks is enhanced when cognitive processing is distributed across the two hemispheres. Moreover, allelic variations in the proteolipid protein 1 gene *PLP1* and the contactin 1 gene *CNTN1* correlated with the extent to which individual performance is enhanced by interhemispheric integration. Variation in myelin genes possibly affects the microstructure of the corpus callosum by altering oligodendrocyte structure. Therefore, these results provide a foundation for understanding how genetics plays a role in modulating the efficacy of transcallosal transmission.

Keywords White matter · Interhemispheric transfer · Oligodendrocytes · Brain structure · Transcallosal transmission

Introduction

During cognitive processing, large amounts of information are transferred back and forth between the two hemispheres via the corpus callosum (CC) or further smaller commissures [1–5]. On the behavioral level, interhemispheric integration processes can be assessed with the Banich-Belger Task [6] (see "Methods" section for details). Interestingly, the results of this task show that there are considerable interindividual differences in the extent to which interhemispheric processing is advantageous when performing a demanding cognitive task [6, 7], indicating that some participants show more interhemispheric integration than others. Since interhemispheric transfer is mostly conducted over the CC [8], these findings strongly suggest that there are interindividual differences in transcallosal efficacy (e.g., regarding the speed of interhemispheric transfer). However, the molecular basis of these interindividual differences in callosal efficacy is still unclear. In principle, there are two main factors that modulate the velocity of interhemispheric conduction. On the one hand, conduction speed is proportional to the diameter of the axon [9], with thicker axons transmitting neuronal information faster. On the other hand, interhemispheric transfer time is critically

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modulated by myelination of the involved axonal fibers. Myelinated axons conduct neuronal information faster than unmyelinated axons of the same diameter [10], and patients with demyelinating diseases typically show slower interhemispheric transfer than controls. For example, patients with multiple sclerosis have longer interhemispheric transfer times than healthy controls [11, 12]. Similarly, patients with Marchiafava-Bignami disease, an alcoholism-related disorder that is characterized by CC demyelination, also show reduced interhemispheric transfer [13]. Due to this link between myelination and interhemispheric transfer time, 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 interindividual differences in interhemispheric integration. One of the main genes identified in this regard is *PLP1*, which encodes the proteolipid protein, one of the major myelin proteins in the central nervous system [14]. Mutations in this gene have been found to cause two types of dysmyelinating leukodystrophies, X-linked Pelizaeus-Merzbacher disease, and hereditary spastic paraplegia type 2 [15]. The other major myelin protein is the myelin basic protein, encoded by *MBP*. Together, PLP1 and MBP constitute about 80% of the overall protein mass of myelin [14–16]. Further, myelin-related genes include *MOG* which encodes the myelin oligodendrocyte glycoprotein [17], the myelin-associated oligodendrocyte basic protein gene *MOBP* [18], the contactin 1 gene *CNTN1* that has been related to oligodendrocyte differentiation [19], and the glycoprotein M6A gene *GPM6A* which belongs to the myelin proteolipid protein family [20].

The aim of the present study was to examine the potential role of allelic variations in these myelin-associated genes for interhemispheric integration. We, therefore, genotyped 18 single nucleotide polymorphisms (SNPs) within *PLP1*, *GPM6A*, *MOG*, *MBP*, *CNTN1*, and *MOBP* (see Table 3) in a sample of 453 healthy adult German students and correlated the responding genotypes with a behavioral performance marker of interhemispheric integration.

Methods

Participants

Overall, 453 healthy adults (263 women and 190 men) of Caucasian descent for at least two generations participated in the present study. All participants were genetically unrelated as determined by self-assessment. The participants were mainly university students, and mean age was 23.94 years (range 18–34). All participants were native German speakers and right-handed as tested with the Edinburgh Handedness Inventory [21] (mean lateralization quotient 82.02, standard deviation 17.53). They gave written informed consent and were treated in accordance with the Declaration of Helsinki. The study was approved by the ethics committee of the Ruhr-University Bochum.

Genotyping

For noninvasive sampling, exfoliated cells were brushed from the oral mucosa of the participants. DNA isolation was performed with QIAamp DNA mini Kit (50) (Qiagen GmbH, Hilden, Germany). SNP genotyping was conducted by polymerase chain reaction (PCR) and differential enzymatic analysis with the PCR restriction fragment length polymorphism method (PCR-RFLP methodology in [22]). A total of 18 SNPs were selected from dbSNP (www.ncbi.nlm.nih.gov/projects/SNP/) based on potential involvement in myelinization: *PLP1* rs2233696, rs1126707, rs2294152, rs1599989, rs17003884, and rs521895; *GPM6A* rs10520303 and rs1495717; *MOG* rs3130250, rs2857766, and rs3130253; *MBP* rs470797; *CNTN1* rs1056019, rs935105, rs7305733, rs11179136, and rs11179347; and *MOBP* rs3748988. We selected coding SNPs in candidate genes with a minor allele frequency of 0.10 based on data from the NCBI dbSNP database for the Caucasian population. If coding SNPs with a MAF >0.1 were not available for analysis, intronic SNPs were selected. Details about selected SNPs are listed in Supplementary Table 1. In genes, where a statistically significant association with behavioral performance could be detected, additional four or five tagging SNPs (Haploview Software: [23]) were selected and analyzed in the genes PLP1 and CNTN1 based upon results of this study. Haploblock structures are shown in Supplementary Fig. 1. Further details of methodology and primer sequences are available upon request.

Banich-Belger Task

To assess interhemispheric integration, we used a paradigm adapted from Banich and Belger [6] which has previously been used by Bayer et al. [7]. At the beginning of each trial, participants were asked to fixate a cross in the middle of the screen. Then, a stimulus array consisting of three letters arranged in triangular shape was presented around a central fixation cross. The top two stimuli were always two different uppercase letters, one in the left visual field (LVF) and the other one in the right visual field (RVF). These letters were presented 2.8° of visual angle lateral from the midline and 1.4° visual angle above the fixation cross. A third letter was presented 1.4° visual angle below the fixation point and 1.4° visual angle either to the right or left of the center. Participants are instructed to indicate whether or not the target letter matches one of the probe letters. The paradigm consisted of two different

tasks: In the physical-identity task, the third letter was an uppercase letter, and participants were asked to indicate whether the bottom letter was physically identical to one of the top two letters. In the name-identity task, the bottom letter was a lowercase letter, and participants determined whether this had the same name as either of the top two letters. This task is more demanding than the physical-identity task, since an additional cognitive processing step is required. Letter stimuli were A, B, E, G, H, Q, R, T, and, in the name-identity task, also their lowercase equivalents. Each trial started by presentation of a fixation cross for 200 ms, followed by a stimulus array for 200 ms and then by an intertrial interval of randomized length between 500 and 2000 ms in which responses were recorded. The ITI was jittered to avoid preparation effects. Both tasks comprised 224 trials divided into four blocks of 56 trials each, with brief breaks between blocks. All stimuli appeared with the same frequency. The participants responded with either the right or left index finger on alternating blocks. The head of the participants was placed in a chin rest to avoid head movements and thus distortions of the visual half-field stimulation manipulation. The order of hand use was balanced between subjects. Prior to each task, participants performed 28 practice trials which were excluded from analysis. Within each block, half of the trials were match trials (target and probe were identical). Half of these match trials were across trials (target and probe were presented in different visual half-field), while the other half were within trials (target and probe were presented in the same visual half-field). Within both types of matches, the bottom letter appeared equally often in the RVF and LVF. Typically, on the physical-identity task, participants are faster on within trials, while on the name-identity task, they are faster on across trials. This effect is thought to reflect the advantage of interhemispheric over unihemispheric processing with increasing task demands [6].

Statistical Analyses

Median reaction times (RT) on correct trials and the number of correct trials were used as dependent variables. Median RT was chosen due to its statistical robustness regarding outliers. For both the physical- and the name-identity task, an across field advantage (AFA) was calculated for both RTs and the number of correct trials as the difference between trial types (within trials minus across trials). For the calculation of AFAs, only match trials were analyzed because mismatch trials cannot be categorized as across- or within-field trials. The statistical analyses were performed assuming a codominant effect for each polymorphism. Thus, all genotype groups were analyzed separately. Bonferroni correction was chosen to correct for multiple comparisons.

Results

To test whether the typical pattern of results in the Banich-Belger Task was replicated in the present study, the data were first analyzed without taking the participants' genotypes into account by using a 2 × 2 repeated measures ANOVA with task (physical-identity task and name-identity task) and trial type (within-field trial, across-field trial) as within-participants factors. For the number of correct trials (see Table 1 for descriptive statistics), the ANOVA revealed a main effect of task ($F_{(1, 450)} = 359.36$; $p < 0.000001$; partial $\eta^2 = 0.44$), indicating that participants were more accurate in the easier physical-identity task (52.8 ± 0.12) than in the more demanding name-identity task (50.12 ± 0.17). Moreover, a significant task by trial type interaction emerged ($F_{(1, 450)} = 50.72$; $p < 0.000001$; partial $\eta^2 = 0.10$), indicating that on the physical-identity task, participants were more accurate in within field (53.09 ± 0.13) compared to across field trials (52.50 ± 0.14), while the opposite pattern was observed on the name-identity task (within field trials 50.01 ± 0.20; across field trials 50.82 ± 0.17). The main effect of trial type failed to reach significance ($F_{(1, 450)} = 0.97$; $p = 0.33$).

For median RT (see Table 2 for descriptive statistics), the ANOVA revealed a main effect of task ($F_{(1, 450)} = 1532.07$; $p < 0.000001$; partial $\eta^2 = 0.77$), indicating that participants were faster in the easier physical-identity task (443.61 ± 3.46) than in the more demanding name-identity task (594.13 ± 5.69). Additionally, a main effect of trial type emerged ($F_{(1, 450)} = 19.41$; $p < 0.00001$; partial $\eta^2 = 0.04$), indicating that participants were faster on across field trials (515.48 ± 4.32) than on within field trials (522.27 ± 4.42). This effect was modulated by the factor task, as indicating by a significant task by trial type interaction ($F_{(1, 450)} = 355.20$; $p < 0.000001$; partial $\eta^2 = 0.44$). This interaction showed that participants were faster on within field trials (433.90 ± 3.52) compared to across field trials (453.33 ± 3.57) on the physical-identity task, while this pattern was reversed on the name-identity task (within field trials 610.65 ± 5.96; across field trials 577.62 ± 5.70). Taken together, this analysis showed that we replicated the typical pattern of results in the Banich-Belger Task in our sample [6].

In order to investigate the specific effects of genetic variation in the analyzed candidate genes on interhemispheric integration, the AFAs were subsequently analyzed using 2 × 3 (2 × 5 for *PLP1*, since *PLP1* is located on the X chromosome). Thus, there are five instead of three genotype groups; e.g., men T and C; women TT, CT and CC) repeated measures ANOVA with task (physical-identity task and name-identity task) as within-participants factor and genotype as between-participants factor (see Table 3 for number of correct trials and Table 4 for RT).

Overall, three effects reached significance at the 0.0027 level (0.05/18, the number of tested SNPs; Bonferroni

Table 1 Number of correct trials in the Banich-Belger Task

Task	Within-field trials	Across-field trials	AFA
Physical-identity	53.09 ± 0.13	52.50 ± 0.14	0.59 ± 0.14
Name-identity	50.01 ± 0.20	50.82 ± 0.17	−0.81 ± 0.16

correction) so that they were significant after correction for multiple comparisons.

For number of correct trials, the interaction genotype by task reached significance for the *CNTN1* rs1056019 SNP ($F_{(2,\ 446)} = 8.38$; $p = 0.0002$; $\eta^2 = 0.04$; see Fig. 1 for mean AFA's and standard errors). This effect was also observed if a dominant model was assumed ($p = 0.0036$, $\eta^2 = 0.02$). In the physical-identity task, all three genotype groups were more accurate on within than on across trials (CC 0.39 ± 0.33; CT 0.48 ± 0.22; TT 0.81 ± 0.21), and post hoc tests revealed no significant differences between the groups (all p's > 0.27). For the name-identity task, however, only the CT (−0.93 ± 0.25) and TT (−1.29 ± 0.25) genotype groups showed the typical pattern of being more accurate in the across condition, while the CC genotype was more accurate in the within condition (0.55 ± 0.38). Post hoc tests revealed this group to be significantly different from the two other groups (CC vs. CT: $p = 0.001$; CC vs. TT: $p = 0.00006$).

For RT, the interaction genotype by task reached significance for the *PLP1* SNP, rs1126707 ($F_{(4,\ 445)} = 4.39$; $p = 0.0017$; $\eta^2 = 0.04$; see Fig. 2 for mean AFAs and standard errors). On the physical-identity task, all five genotype groups were faster on within than on across trials (T −15.82 ± 2.74; C −13.61 ± 3.84; TT −23.19 ± 2.54; CT −18.75 ± 3.28; CC −30.43), and post hoc tests revealed that the TT ($p = 0.049$) and the CC group ($p = 0.03$) had significantly larger negative AFAs than the T group. Moreover, the TT ($p = 0.04$) and the CC group ($p = 0.02$) had significantly larger negative AFAs than the C group. On the name-identity task, all five genotype groups were faster on across than on within trials (T 20.27 ± 4.79; C 39.74 ± 6.72; TT 37.64 ± 4.43; CT 34.46 ± 5.73; CC 46.63 ± 10.75). Here, post hoc tests revealed that the T group had significantly smaller AFAs than the C group ($p = 0.02$), the CC group ($p = 0.03$), and the TT group ($p = 0.008$).

Moreover, the interaction reached significance for the *PLP1* rs521895 SNP ($F_{(4,\ 444)} = 4.42$; $p = 0.0016$; $\eta^2 = 0.04$; see Fig. 3 for mean AFAs and standard errors).

Table 2 Median RT (in ms ± standard error) in the Banich-Belger Task

Task	Within-field trials	Across-field trials	AFA
Physical-identity	433.90 ± 3.52	453.33 ± 3.57	−19.43 ± 1.46
Name-identity	610.65 ± 5.96	577.62 ± 5.70	32.90 ± 2.54

On the physical-identity task, all five genotype groups were faster on within than on across trials (A −14.17 ± 4.33; G −14.77 ± 2.65; AA −18.62 ± 5.56; AG −23.95 ± 2.85; GG −22.81 ± 2.91). Post hoc tests revealed that this difference was significantly smaller in the G group than in the AG ($p = 0.19$) and GG group ($p = 0.042$). All other comparisons failed to reach significance (all p's > 0.06). On the name-identity task, all five genotype groups were faster on across than on within trials (A 16.77 ± 7.53; G 30.51 ± 4.61; AA 24.86 ± 9.66; AG 34.15 ± 4.95; GG 43.96 ± 5.06). Here, post hoc test revealed that the GG group had significantly larger AFAs than the A group ($p = 0.003$). All other comparisons failed to reach significance (all $p > 0.05$).

As several authors suggest a role of interhemispheric interaction via the CC for the emergence of functional hemispheric asymmetries [4], we also conducted an explorative analysis of the handedness data in relation to the genotypes of the investigated SNPs (see Table 5). The lowest p value was observed for *CNTN1* rs935105 ($p = 0.07$), but none of the effects reached the corrected significance level.

Discussion

Understanding the genetic determinants of interhemispheric integration will advance our understanding on the structural neural blueprint that modulates cortical systems interactions during cognitive task execution. Myelination is a key factor to increase speed of interhemispheric transfer [10]. Therefore, it was the aim of the present study to explore the role of myelin-related genes in the Banich-Belger Task that assesses interhemispheric transfer. We report significant associations between allelic variations in myelin genes and the extent of interhemispheric integration.

In accordance with previous studies [6, 7], we show the expected pattern of results in this task in a very large sample of more than 400 healthy adults: Participants were more accurate and faster on the physical-identity task, confirming the assumption that this task is less demanding than the name-identity task. Moreover, performance on both tasks was modulated by trial type. On the physical-identity task, participants were faster and more accurate on within field trials compared to across field trials, indicating that they did not benefit from interhemispheric integration on this type of task. In contrast, the reverse pattern was observed on the name-identity task. Here, participants did indeed benefit from interhemispheric integration, as indicated by the finding that they were faster and more accurate on across-trials than on within-trials. Moreover, in accordance to the findings from Banich and Belger [6], we also showed that division of processing between the two hemispheres leads to faster performance. Taken together, these findings lend further support to the idea

Table 3 Results of the Banich-Belger Task for the different genotyped SNPs: AFAs for number of correct trials as dependent variable

Gene	SNP	ME task	ME genotype	Interaction
PLP1	rs2233696	$p < 0.001$; $\eta^2 = 0.11$	$p = 0.64$	$p = 0.54$
	rs1126707	$p < 0.001$; $\eta^2 = 0.09$	$p = 0.12$	$p = 0.42$
	rs2294152	$p < 0.001$; $\eta^2 = 0.09$	$p = 0.24$	$p = 0.06$
	rs1599989	$p = 0.15$	$p = 0.46$	$p = 0.04$; $\eta^2 = 0.02$
	rs17003884	$p < 0.001$; $\eta^2 = 0.03$	$p = 0.61$	$p = 0.33$
	rs521895	$p < 0.001$; $\eta^2 = 0.07$	$p = 0.29$	$p = 0.46$
GPM6A	rs10520303	$p = 0.06$	$p = 0.55$	$p = 0.59$
	rs1495717	$p < 0.001$; $\eta^2 = 0.05$	$p = 0.03$; $\eta^2 = 0.02$	$p = 0.19$
MOG	rs3130250	$p < 0.001$; $\eta^2 = 0.03$	$p = 0.69$	$p = 0.84$
	rs2857766	$p < 0.001$; $\eta^2 = 0.04$	$p = 0.63$	$p = 0.73$
	rs3130253	$p = 0.45$	$p = 0.85$	$p = 0.80$
MBP	rs470797	$p < 0.001$; $\eta^2 = 0.03$	$p = 0.25$	$p = 0.94$
CNTN1	rs1056019	$p < 0.001$; $\eta^2 = 0.06$	$p = 0.06$	**$p = 0.0002$; $\eta^2 = 0.04$**
	rs935105	$p < 0.001$; $\eta^2 = 0.03$	$p = 0.16$	$p = 0.54$
	rs7305733	$p < 0.001$; $\eta^2 = 0.10$	$p = 0.49$	$p = 0.08$
	rs11179136	$p < 0.001$; $\eta^2 = 0.04$	$p = 0.13$	$p = 0.08$
	rs11179347	$p < 0.001$; $\eta^2 = 0.11$	$p = 0.24$	$p = 0.007$; $\eta^2 = 0.02$
MOBP	rs3748988	$p < 0.001$; $\eta^2 = 0.07$	$p = 0.69$	$p = 0.10$

For nominally significant effects, partial η^2 is provided as an estimator of effect size. All effects with a p value below 0.0027 (the corrected level of significance) are given in bold

that performance on cognitively demanding tasks is enhanced when cognitive processing is distributed across the two hemispheres [6].

Interestingly, our data show that the extent to which individual performance during interhemispheric integration is modulated by variation in the genes *PLP1* and *CNTN1*. In *PLP1*, two SNPs were associated with the performance on the Banich-Belger Task. For the intronic rs521895 SNP, the G group showed significantly smaller AFAs in the physical-identity task than the AG or the GG group, showing that men

Table 4 Results of the Banich-Belger Task for the different genotyped SNPs: AFAs for median RT as dependent variable

Gene	SNP	ME task	ME genotype	Interaction
PLP1	rs2233696	$p < 0.001$; $\eta^2 = 0.45$	$p = 0.11$	$p = 0.004$; $\eta^2 = 0.03$
	rs1126707	$p < 0.001$; $\eta^2 = 0.39$	$p = 0.29$	**$p = 0.0017$; $\eta^2 = 0.04$**
	rs2294152	$p < 0.001$; $\eta^2 = 0.36$	$p = 0.51$	$p = 0.005$; $\eta^2 = 0.03$
	rs1599989	$p < 0.001$; $\eta^2 = 0.17$	$p = 0.96$	$p = 0.64$
	rs17003884	$p < 0.001$; $\eta^2 = 0.19$	$p = 0.18$	$p = 0.006$; $\eta^2 = 0.03$
	rs521895	$p < 0.001$; $\eta^2 = 0.34$	$p = 0.44$	**$p = 0.0016$; $\eta^2 = 0.04$**
GPM6A	rs10520303	$p < 0.01$; $\eta^2 = 0.15$	$p = 0.86$	$p = 0.92$
	rs1495717	$p < 0.001$; $\eta^2 = 0.21$	$p = 0.49$	$p = 0.88$
MOG	rs3130250	$p < 0.001$; $\eta^2 = 0.17$	$p = 0.93$	$p = 0.97$
	rs2857766	$p < 0.001$; $\eta^2 = 0.20$	$p = 0.04$; $\eta^2 = 0.01$	$p = 0.01$; $\eta^2 = 0.02$
	rs3130253	$p < 0.001$; $\eta^2 = 0.04$	$p = 0.97$	$p = 0.66$
MBP	rs470797	$p < 0.001$; $\eta^2 = 0.20$	$p = 0.05$; $\eta^2 = 0.01$	$p = 0.14$
CNTN1	rs1056019	$p < 0.001$; $\eta^2 = 0.39$	$p = 0.35$	$p = 0.15$
	rs935105	$p < 0.001$; $\eta^2 = 0.11$	$p = 0.15$	$p = 0.60$
	rs7305733	$p < 0.001$; $\eta^2 = 0.40$	0.29	$p = 0.07$
	rs11179136	$p < 0.001$; $\eta^2 = 0.07$	$p = 0.74$	$p = 0.58$
	rs11179347	$p < 0.001$; $\eta^2 = 0.40$	$p = 0.40$	$p = 0.26$
MOBP	rs3748988	$p < 0.001$; $\eta^2 = 0.39$	$p = 0.29$	$p = 0.51$

For nominally significant effects, partial η^2 is provided as an estimator of effect size. All effects with a p value below 0.0027 (the corrected level of significance) are given in bold

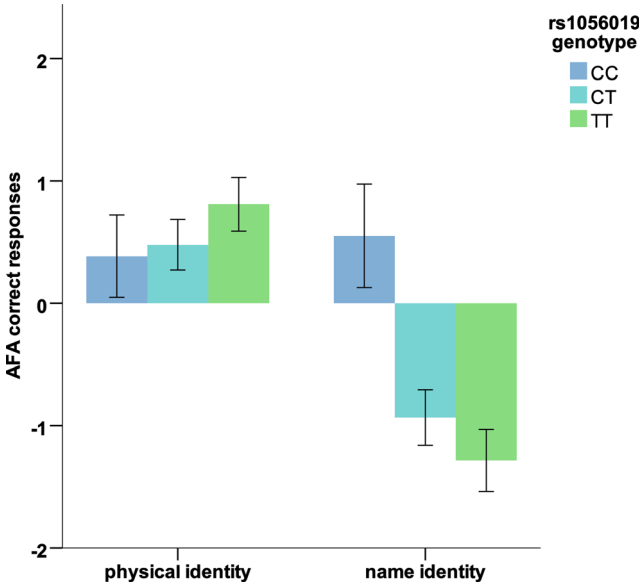

Fig. 1 Association of *CNTN1* rs1056019 genotypes and performance on the Banich-Belger Task (AFAs for number of correct trials). *Error bars* show standard errors. *CNTN1* rs1056019 genotypes had the following Ns: CC 78, CT 184, and TT 189

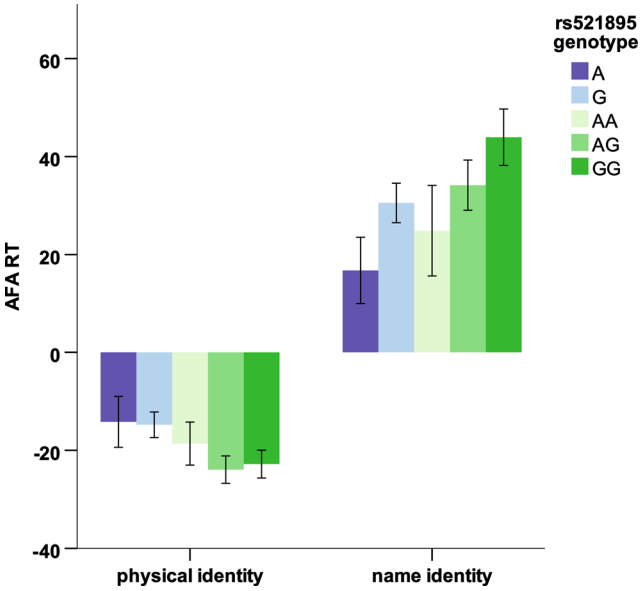

Fig. 3 Association of *PLP1* rs521895 genotypes and performance on the Banich-Belger Task (AFAs for median RT in ms). *Error bars* show standard errors. *PLP1* rs521895 genotypes had the following Ns: A 51, G 136, AA 31, AG 119, and GG 114

hemizygous for the G allele benefited less from interhemispheric integration than women heterozygous or homozygous for the G allele. On the name-identity task, the GG group had significantly larger AFAs than the A group, indicating that cognitive processing in CC women benefited significantly more from interhemispheric integration than in A men. For the rs1126707 SNP, the analysis revealed that on the physical-identity task, the TT and the CC group had significantly larger negative AFAs than the two male groups T and C, possibly indicating a sex difference on this task, with men having smaller AFAs than homozygous women, independent of genotype. On the name-identity task, this was not the case. Here, the T group had significantly smaller AFAs than the C group, the CC group, and the TT group, with larger absolute differences between the T group and the C group (−19.46) and the

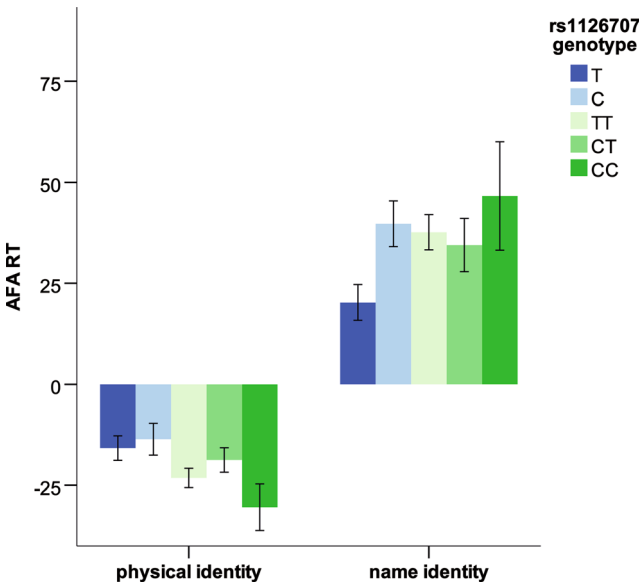

Fig. 2 Association of *PLP1* rs1126707 genotypes and performance on the Banich-Belger Task (AFAs for median RT in ms). *Error bars* show standard errors. *PLP1* rs1126707 genotypes had the following Ns: T 126, C 64, TT 149, CT 88, and CC 25

Table 5 Results of the Edinburgh Handedness Inventory for the different genotyped SNPs

Gene	SNP	Handedness LQ
PLP1	rs2233696	$p = 0.48$
	rs1126707	$p = 0.56$
	rs2294152	$p = 0.15$
	rs1599989	$p = 0.82$
	rs17003884	$p = 0.77$
	rs521895	$p = 0.99$
GPM6A	rs10520303	$p = 0.65$
	rs1495717	$P = 0.62$
MOG	rs3130250	$P = 0.89$
	rs2857766	$p = 0.11$
	rs3130253	$p = 0.14$
MBP	rs470797	$p = 0.47$
CNTN1	rs1056019	$p = 0.23$
	rs935105	$p = 0.07$
	rs7305733	$p = 0.40$
	rs11179136	$p = 0.36$
	rs11179347	$p = 0.41$
MOBP	rs3748988	$p = 0.82$

LQ laterality quotient

CC group (−26.36) than between the T and the TT group (−17.36). While these results are not as clear-cut as for the rs521895 variation, they indicate that at least for men, carriers of the rare C allele benefit significantly more from interhemispheric integration on the name-identity task than men with the T allele. Interestingly, the synonymous SNP rs1126707 that induces no amino acid change occurs in a binding site for a specific serine/arginine-rich ESE protein (SR ESEs) [24].

In addition to the findings in *PLP1*, performance on the Banich-Belger Task was also modulated by genotypes of the exonic SNP rs1056019 (N472N), which leads to the synonymous exchange of an asparagine in *CNTN1*. While no accuracy differences between genotype groups were observed for the physical-identity task, the homozygous CC group was significantly different from carriers of at least one T allele on the name-identity task. While the latter showed typical results on this task, being more accurate in the across-condition, the homozygous CC group was more accurate in the within-condition. Thus, performance of these participants was not enhanced but decreased by interhemispheric integration, probably indicating less efficient interhemispheric transfer over the CC in this genotype than in carriers of the T allele.

Although the potential functional role of the synonymous *CNTN1* SNP remains elusive, our results support the assumption that variation in *CNTN1* could influence the efficacy of interhemispheric integration over the CC. *CNTN1*, located on 12q11-q12, is a member of the immunoglobulin (Ig) gene family and encodes a glycosylphosphatidylinositol-anchored neuronal membrane protein that functions as a cell adhesion molecule [25]. Contactin has been shown to act as a modulator of neurogenesis during cerebral cortex development [26] and is involved in oligodendrocyte precursor development and differentiation [27]. Further evidence for a functional role of cell adhesion for the development of cortical structures involved in interhemispheric integration and hemispheric asymmetries come from clinical studies in Van Maldergem syndrome [28].

Thus, variation in *CNTN1* could modulate the efficacy of interhemispheric transmission by altering the microstructure of myelin in the CC. As for the *CNTN1* rs1056019 SNP, the functional roles of the two associated *PLP1* SNPs remain to be identified, but our results support the assumption that variation in *PLP1* could influence the efficacy of interhemispheric integration via the CC. *PLP1* is located on Xq22 and encodes the proteolipid protein and its splicing variant DM20, two hydrophobic transmembrane proteins that are mainly expressed in oligodendrocytes [29, 30]. Proteolipid protein plays a major role in myelin sheath formation by promoting sheath compaction [29] and has also been found to be functionally involved in stabilization and maintenance of myelin sheaths as well as oligodendrocyte development and axonal survival [31]. Mutations in *PLP1* have been found to cause two types of dysmyelinating leukodystrophies in the central nervous system, Pelizaeus-Merzbacher disease, and Hereditary spastic paraplegia type 2 [15]. A recent diffusion tensor imaging study in a *PLP1* transgenic mouse model for Pelizaeus-Merzbacher disease showed that fractional anisotropy in the CC is significantly reduced in this disease [32]. Unfortunately, no functional studies on the relation of callosal microstructure and behavioral performance measures of interhemispheric integration have as yet been conducted in human patients with Pelizaeus-Merzbacher disease. However, research in patients with multiple sclerosis shows that degeneration of myelin sheaths critically impacts the relation between microstructure of the CC, as reflected by fractional anisotropy and interhemispheric transmission [33]. A recent study supports the myelin hypothesis by showing a strong association between fractional anisotropy in the CC and bound pool fraction, a more direct measure of myelin content in white matter fiber tracts [34]. Therefore, it can be assumed that callosal myelination has an impact on performance on interhemispheric integration tasks. This idea is also supported by studies linking myelination of callosal fibers to the BOLD response on interhemispheric transfer tasks. For example, Fornari et al. [35] investigated spatial integration over the CC in children aged between 7 and 13 years using a combined magnetization transfer imaging (MTI) and fMRI protocol. They could show that the intensity and extent of individual BOLD responses in lingual gyri in both hemispheres were positively correlated with the degree of myelination in the posterior part of the CC interconnecting visuo-parietal areas. Moreover, two studies in adults showed a significant relation between interhemispheric transfer time measured with EEG and microstructural properties of the corpus callosum, implying that white matter integrity in the corpus callosum directly affects the efficacy of interhemispheric transfer [36, 37]. Thus, there is a direct link between callosal myelination and cognitive functioning that needs interhemispheric transfer and integration. Possibly, variation in myelin genes affects the microstructure of the CC, thus modulating the efficacy of callosal transmission and therefore the extent of interhemispheric integration during a complex cognitive task.

In conclusion, the results of this analysis suggest that *PLP1* and *CNTN1* might be involved in the efficiency of interhemispheric integration. However, our approach should be regarded as an initial screen where a predefined selection of SNPs was genotyped in a small proportion of myelin-related candidate genes. Our selection mainly included SNPs located in coding regions of the candidate genes but does not provide coverage across genes and variation outside of noncoding regions. Other SNPs in the analyzed genes could also importantly contribute to the measured phenotypes but were not assessed here outlining the major limitations of our study. Moreover, other genes that are involved in myelination were not assessed and possibly contribute to a behavioral phenotype, too. A detailed follow-up should include complete

characterization of the analyzed genes using a combination of further SNPs. Moreover, additional genes involved in myelination should also be analyzed in the future. Although SNP selection was based on a MAF >0.1, only a small proportion of individuals seem to have driven some of the significant effects, e.g., for rs1126707. This issue needs to be addressed by future replication studies in larger cohorts.

Taken together, our findings support the assumption that interhemispheric transmission via the CC might be influenced by genetic variability in *PLP1* and *CNTN1*. While the exact amount of variance variation in these genes can explain should be investigated in future replication studies in larger cohorts, our effect sizes indicate that the interhemispheric transmission is a complex phenotype that is modulated by heterogeneous genetic and possibly nongenetic factors.

The current report, although explorative in nature, may serve as a basis for further studies in other cohorts and as a basis for detailed SNP genotyping of the analyzed genes. Since the efficacy of interhemispheric transmission has been suggested to modulate hemispheric asymmetries (for a review see [38]), this finding may be particularly interesting in the context of the ongoing discussion about the genetic determinants of lateralization, even though we did not observe an effect for handedness [39–44]. Future studies should recruit larger cohorts to independently replicate these findings and to allow for analysis of a wider range of candidate SNPs as well as their possible interactions. Another interesting suggestion for future work would be not only to use a behavioral measure of interhemispheric integration like the Banich-Belger Task but also to determine fractional anisotropy of the CC using diffusion tensor imaging, in order to get an actual measure of callosal microstructure. Applying this enhanced protocol in healthy participants as well as in patients with leukodystrophies like Pelizaeus-Merzbacher disease and other demyelinating diseases like multiple sclerosis could yield further insights into the complex relation of myelin genes, callosal microstructure, and interhemispheric integration.

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