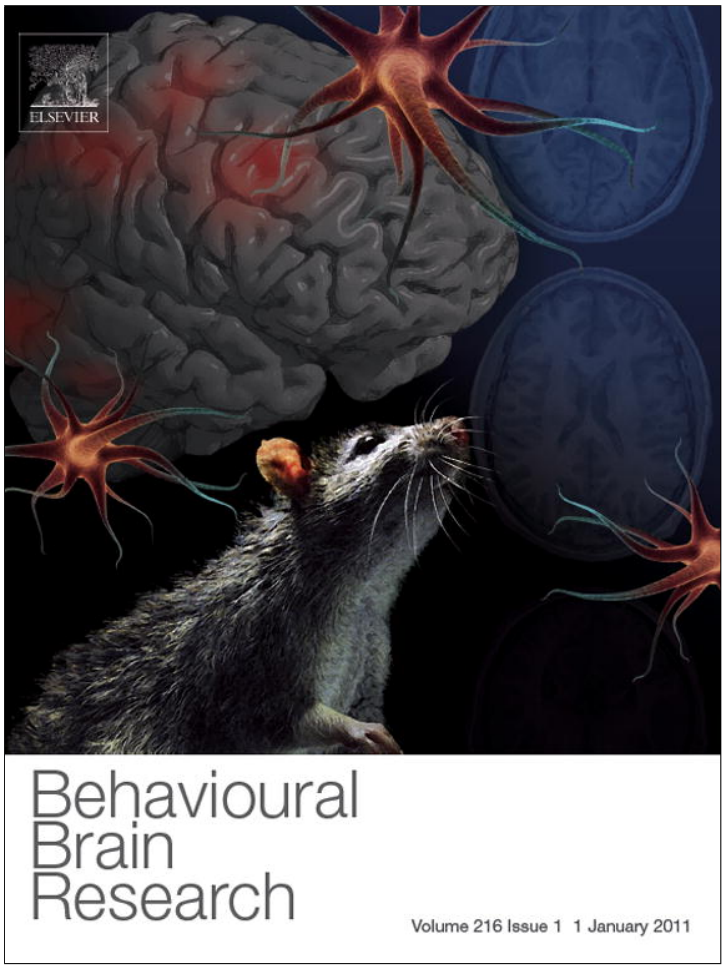
Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



(This is a sample cover image for this issue. The actual cover is not yet available at this time.)

This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

http://www.elsevier.com/copyright

Author's personal copy

Behavioural Brain Research 225 (2011) 284–289

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Variation in the NMDA receptor 2B subunit gene *GRIN2B* is associated with differential language lateralization

Sebastian Ocklenburg[a,*], Larissa Arning[b], Constanze Hahn[a], Wanda M. Gerding[b], Jörg T. Epplen[b], Onur Güntürkün[a], Christian Beste[a]

[a] *Institute of Cognitive Neuroscience, Biopsychology, Department of Psychology, Ruhr-University of Bochum, Bochum, Germany*
[b] *Department of Human Genetics, Ruhr-University of Bochum, Bochum, Germany*

ARTICLE INFO

Article history:
Received 31 May 2011
Received in revised form 16 July 2011
Accepted 23 July 2011

Keywords:
NMDA
Glutamate
Functional cerebral asymmetries
Brain asymmetry

ABSTRACT

Variations in the *N-methyl-D-aspartate receptor 2B subunit* gene (*GRIN2B*) have been associated with schizophrenia, a psychiatric disorder associated with reduced left-hemispheric language dominance. Here, we investigated, whether different polymorphisms in *GRIN2B* influence language lateralization and handedness in healthy individuals. In a cohort of 424 genetically unrelated participants we found significant association between the synonymous *GRIN2B* variation rs1806201 and language lateralization assessed using the dichotic listening task. Individuals carrying the heterozygous CT genotype exhibited more pronounced left-hemispheric language dominance as compared to both homozygous CC and TT individuals. Such an association was not identified for handedness. These findings suggest that variation in NMDA-receptors contributes to the interindividual variability of language lateralization.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

Lateralization of brain and behavior is a common feature in vertebrates [1–3] with handedness and language lateralization being the two most prominent examples in humans [4]. In 95% of the right-handers and 75% of the left-handers the left hemisphere is dominant for language processing [5,6]. Due to this high correlation in the majority of the population, several authors suggested a common genetic background for handedness and language lateralization (e.g. Refs. [7,8]). This view, however, has been questioned by a number of recent findings that suggest at least partly independent polygenic mechanisms for the inheritance of language lateralization and handedness [9–11].

The most widely used paradigm to assess language lateralization is the dichotic listening task (DLT; [12]). In this paradigm, two different auditory stimuli (typically short consonant–vowel syllables like BA or GA) are presented simultaneously, one to each ear. Probands are asked to report the stimulus they heard best and typically a clear right ear advantage is observed. This fact is interpreted as a behavioral measure for left-hemispheric dominance for the processing of verbal information [12], an explanation that is supported by the high correlation between the results of the DLT and the Wada test [13]. Moreover, a strong association between performance in the DLT and asymmetric brain activity has been reported by several neuroimaging studies [14–18].

On a molecular level, it has been suggested that glutamatergic neurotransmission is of particular importance for language lateralization [19–21]. For example, Hugdahl et al. [19] reported reduced right-ear advantage in the DLT after administration of memantine, a drug that reduces the action of glutamate at the N-methyl D-aspartate (NMDA) receptor. NMDA-receptors consist of heteromeric complexes, which comprise an obligatory NR1 subunit as well as additional NR2A-D and NR3A-B subunits [22].

The NMDA receptor class is involved in several forms of synaptic plasticity, which have been linked to cognitive processes related to learning and memory [23] and especially NR2B receptor subunits have been found to be associated with cognitive functions in mice [24] and humans. For example, a recent study observed a selective modulation of response inhibition processes by variation in the *GRIN2B* rs1806201 SNP [25]. In this study, stronger response inhibition processes were found in the combined CT/TT (C: cytosine; T: thymine) genotype group, compared to the CC genotype group. In addition, a recent study investigating how variation in *GRIN2B* influences decision making using the Iowa gambling task found that women with a CC allele in the rs1806201 SNP made less use of a win–stay strategy in this task and demonstrated more exploratory behavior during task execution, indicating a relevance of *GRIN2B* for decision making processes [26]. Moreover, variations in the NMDA receptor 2B subunit gene (*GRIN2B*) have been linked to schizophrenia [27,28], a psychiatric disorder associated with a reduced right ear advantage in the DLT [29,30]. These lines of

* Corresponding author at: Abteilung Biopsychologie, Institut für Kognitive Neurowissenschaft, Fakultät für Psychologie, Ruhr-Universität Bochum, Universitätsstraße 150, 44780 Bochum, Germany. Tel.: +49 234 32 26804; fax: +49 234 32 14377.
E-mail address: sebastian.ocklenburg@rub.de (S. Ocklenburg).

0166-4328/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbr.2011.07.042

Author's personal copy

Table 1
Results of the dichotic listening task for the different *GRIN2B* SNPs. Only for significant effects only the effect sizes are given as the proportion of variance accounted for (partial η^2).

dB SNP rs number	Main effect side	Main effect genotype	Interaction side × genotype
rs1805476	$p < 0.001$; $\eta^2 = 0.59$	$p = 0.32$	$p = 0.07$
rs1805503	$p < 0.001$; $\eta^2 = 0.20$	$p = 0.81$	$p = 0.18$
rs1805247	$p < 0.001$; $\eta^2 = 0.42$	$p = 0.34$	$p = 0.29$
rs1806191	$p < 0.001$; $\eta^2 = 0.55$	$p = 0.31$	$p = 0.28$
rs1806201	$p < 0.001$; $\eta^2 = 0.60$	$p = 0.80$	$p = 0.002$; $\eta^2 = 0.02$
rs3026159	$p < 0.001$; $\eta^2 = 0.47$	$p = 0.66$	$p = 0.31$
rs3026160	$p < 0.001$; $\eta^2 = 0.45$	$p = 0.19$	$p = 0.15$
rs4764011	$p < 0.001$; $\eta^2 = 0.54$	$p = 0.51$	$p = 0.67$
rs10772692	$p < 0.001$; $\eta^2 = 0.54$	$p = 0.23$	$p = 0.31$
rs16909222	$p < 0.001$; $\eta^2 = 0.48$	$p = 0.49$	$p = 0.57$
rs1806194	$p < 0.001$; $\eta^2 = 0.59$	$p = 0.76$	$p = 0.19$
rs1806195	$p < 0.001$; $\eta^2 = 0.56$	$p = 0.79$	$p = 0.44$
rs3026164	$p < 0.001$; $\eta^2 = 0.48$	$p = 0.70$	$p = 0.76$
rs1806213	$p < 0.001$; $\eta^2 = 0.48$	$p = 0.51$	$p = 0.73$

evidence suggest that variation in *GRIN2B* may modulate language lateralization. Therefore, the aim of the present study was to examine the role of *GRIN2B* for handedness and language lateralization. To this end, we genotyped 14 single nucleotide polymorphisms (SNPs) within the 3′ candidate region of *GRIN2B* (see Table 1) in a sample of 424 healthy German students and examined the association of these SNPs with handedness and language lateralization.

2. Methods

2.1. Participants

Overall, 424 genetically unrelated, healthy participants (246 women and 178 men) of Caucasian descent for at least two generations participated in the present study. All participants stated that they had no history of any neurological or psychiatric diseases as assessed by means of a screening questionnaire. The participants had a mean age of 23.75 (range 18–34) and were mainly university students. On average, they had 14.68 (±2.40) years of education. All of them were native German speakers. 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 medical faculty of the Ruhr-University Bochum. Before starting the experiment, hearing thresholds of the participants were screened at 750, 1500 and 3000 Hz using a MA 25 audiometer (MAICO Diagnostic GmbH, Berlin, Germany) in order to ensure normal hearing capability. All individual hearing thresholds ranged below 30 dB and all inter-aural differences fell below 15 dB. All participants were tested with a neuropsychological test battery including a German multiple choice verbal intelligence test (Mehrfachwahl–Wortschatz–Intelligenztest MWT-B) [31], a measure of fluid intelligence (subtest three of the Leistungsprüfsystem LPS) [32] and subtest A and B of the trail-making test as a measure of executive functioning [33]. Participants had an average score of 28.65 (±3.78) in the MWT-B and an average score of 30.73 (±4.56) in the LPS. To complete subtest A of the trail-making test they needed on average 25.13 s (±10.57) and to complete subtest B they needed on average 60.67 s (±32.88). All of these scores indicate normal cognitive functioning in the present sample. As analyzed in ANOVAs, *GRIN2B* genotype groups did not significantly differ in age, years of education or any of the neuropsychological measures (all p's > 0.11).

2.2. Genotyping

For non-invasive sampling, exfoliated cells were brushed from the oral mucosa of the participants. DNA isolation was performed with QIAamp DNA mini Kit (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. In order to investigate the 3′-candidate region of *GRIN2B*, fourteen SNPs were selected spanning 10 kb of this part of the gene. SNPs were primarily selected on the basis of their frequency (MAF > 0.1) from dbSNP (www.ncbi.nlm.nih.gov/projects/SNP/): rs1806213 (IVS10), rs3026164 (IVS10), rs1806195 (IVS10), rs1806194 (IVS10), rs16909222 (IVS11), rs10772692 (IVS11), rs4764011 (IVS11), rs3026160 (Ex12), rs3026159 (IVS12), rs1806201 (Ex13), rs1806191 (Ex13), rs1805247 (Ex13), rs1805503 (3UTR) and rs1805476 (3UTR). Further details of methodology and primer sequences are available upon request.

2.3. Handedness

Handedness was determined using the Edinburgh handedness inventory [34], a widely used ten item questionnaire in which participants are asked to indicate their preferred hand for a number of activities. The laterality quotient (LQ) yielded by the EHI is calculated by $LQ = [(R - L)/(R + L)] \times 100$, with R denoting the number of right-sided preferences and L denoting the number of left-sided preferences. The LQ has a range between +100 and −100, with positive values indicating right handedness and negative values left handedness. In order to also gain a qualitative measure of handedness, participants were grouped into left-handers (LH; LQ between −100 and 0) and right-handers (RH; LQ between 0 and 100). Overall, there were 39 LHs (9.2%) and 385 RHs (90.8%).

2.4. Dichotic listening

Language lateralization was assessed using a verbal DLT with digitally recorded syllable pairs consisting of the six classic consonant–vowel (CV) syllables "BA", "DA", "GA", "KA", "PA" and "TA" as stimuli. Stimuli had a mean duration of 350 ms and were recorded by an adult German male baritone voice. Spectral temporal envelopes of the syllables were matched, and the differences between the voice onset times of the voiced ("BA", "DA", "GA") and voiceless stop consonants ("KA", "PA", "TA") were identified and controlled for. All 30 possible dichotic combinations of the syllable pairs were applied to both ears. Stimuli were administered using Presentation® software (Neurobehavioral Systems, Inc., Albany, USA) and presented using DT 770 Pro headphones (Beyerdynamic GmbH, Heilbronn, Germany) at 80 dB with an interstimulus interval of 2 s. Participants were instructed to press one of six possible keys labeled with the six CV pairs on a customized reaction pad indicating the syllable they perceived. After two practice runs of 12 trials each (which were excluded from later analysis) participants performed four test runs of 30 trials each, resulting in a total of 120 test trials. In order to minimize possible aural differences between the left and the right headphone channels, the headphones were reversed for two of the test runs in counter-balanced order. To account for possible differences between right hand and left hand responses, two of the test runs were answered with each hand in counter-balanced order.

2.5. Statistical analyses

The statistical analyses were performed assuming a co-dominant or a dominant effect for each polymorphism. In the dominant model, the heterozygous and the rarely observed homozygous variation were combined. In the co-dominant model, all three genotypes were analyzed separately. Hardy–Weinberg equilibrium (HWE) was tested for each SNP. The strength of LD between pairs of SNPs was measured as D' by using HAPLOVIEW [http://www.broad.mit.edu/mpg/haploview/]. Haplotypes were determined using the PHASE algorithm [35]. LQs for handedness were analyzed using independent-samples two-sided t-tests. Equality of variances was tested with Levene's test, and the t-tests were corrected if equality of variance was not given. Absolute handedness was analyzed non-parametrically using two-sided χ^2-test. Responses in the DLT were analyzed using repeated-measures' analyses of variance (ANOVA) with the within-subjects factor side (left ear, right ear) and the between-subjects factor genotype.

3. Results

3.1. Dichotic listening

3.1.1. Ear preferences

Altogether, the participants exhibited a clear preponderance of the right (74.95 responses ± 0.95) over the left ear (31.35 responses ± 0.82) as indicated by a main effect of side ($F_{(1,422)} = 637.39$; $p < 0.001$; $\eta^2 = 0.60$). The results of the ANOVAs for the different *GRIN2B* SNPs are reported in Table 1. In order to

Author's personal copy

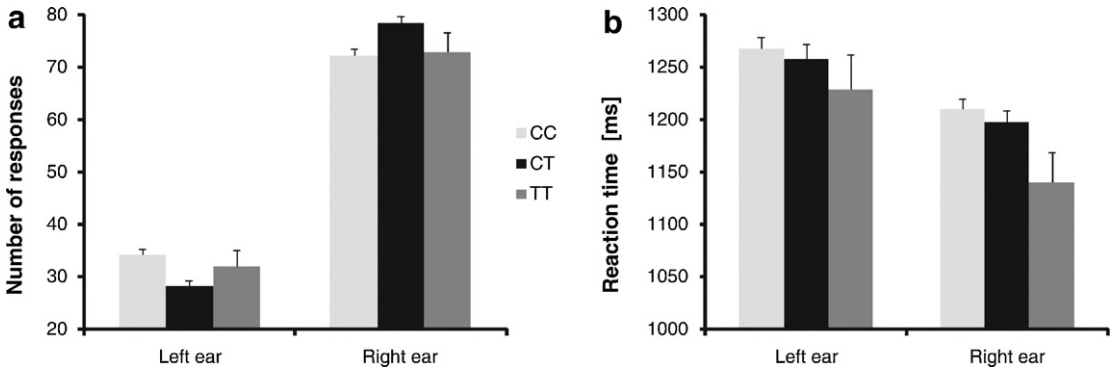


Fig. 1. Association of rs1806201 genotypes and performance in the dichotic listening task. (a) Absolute number of right-ear and left-ear responses. The maximal number of responses was 120. (b) Reaction times in milliseconds (ms) for right-ear and left-ear responses. Error bars show standard error.

investigate possible sex differences regarding the relation of variation in *GRIN2B* and language lateralization the ANOVAs reported in Table 1 were also re-calculated including sex as an additional between-subjects factor. Overall, no sex difference was observed in the DLT ($F_{(1,422)} = 0.30$; $p = 0.86$). Also, none of the interactions between genotype and sex reached significance (all p's > 0.08).

Assuming a dominant effect for each polymorphism, the key interaction side × genotype reached significance for rs1806201 SNP ($F_{(1,422)} = 9.97$; $p < 0.01$; $\eta^2 = 0.02$, Table 1), indicating a considerable difference between right- and left-ear responses in the CT/TT group ($n = 198$; left ear: 28.57 ± 1.19; right ear: 77.62 ± 1.39; difference: 49.05; post hoc test: $p < 0.001$) as compared to the CC group ($n = 226$; left ear: 34.13 ± 1.12; right ear: 72.27 ± 1.30; difference: 38.14; post hoc test: $p < 0.001$). Under the co-dominant model, when all three genotype-groups were analyzed separately (see Fig. 1), the interaction side × genotype ($F_{(1,421)} = 5.81$; $p < 0.01$; $\eta^2 = 0.03$) indicated a more pronounced difference between right and left ear responses in the heterozygous CT individuals ($n = 171$; left ear: 28.05 ± 13.61; right ear: 78.37 ± 17.92; difference: 50.32; post hoc test: $p < 0.001$) as compared to the homozygous CC probands ($n = 226$; left ear: 34.13 ± 18.99; right ear: 72.27 ± 20.85; difference: 38.14; post hoc test: $p < 0.001$) or TT cohort ($n = 27$; left ear: 31.89 ± 15.24; right ear: 72.89 ± 18.40; difference: 41.00; post hoc test: $p < 0.001$). The finding that the interaction was mainly driven by a more pronounced asymmetry in the heterozygous individuals was further confirmed by a comparison of the heterozygous ($n = 171$) against the combined homozygous groups ($n = 253$). Here, the interaction side × genotype was even more pronounced ($F_{(1,422)} = 11.48$; $p < 0.001$; $\eta^2 = 0.03$) indicating a stronger asymmetry in the CT group (left ear: 28.05 ± 13.61; right ear: 78.37 ± 17.92; difference: 50.32.; post hoc test: $p < 0.001$) as compared to the CC/TT group (left ear: 33.89 ± 18.61; right ear: 72.34 ± 20.57; difference: 38.45.; post hoc test: $p < 0.001$). The main effect of genotype did not reach significance ($F_{(1,422)} = 0.06$; $p = 0.80$).

3.1.2. Reaction times

For reaction times, only a main effect of side ($F_{(1,416)} = 109.93$; $p < 0.001$; $\eta^2 = 0.21$) emerged, indicating that participants reacted faster on right ear responses (1199.65 ± 7.51 ms) than on left ear responses (1260.73 ± 8.61 ms). All other main effects and interactions failed to reach significance (all F's < 1.31; all p's > 0.25). There were no significant differences between the two genotype groups regarding misses ($t_{(422)} = 0.25$; $p = 0.80$). Numbers of left- and right-ear responses as well as the reaction times in the DLT are shown in Fig. 1.

3.1.3. Haplotype analysis

Haplotype analysis comprising the seven most frequent SNPs (Fig. 2) predicted five common (frequency >4%) haplotypes, but none of them was associated with language lateralization or handedness.

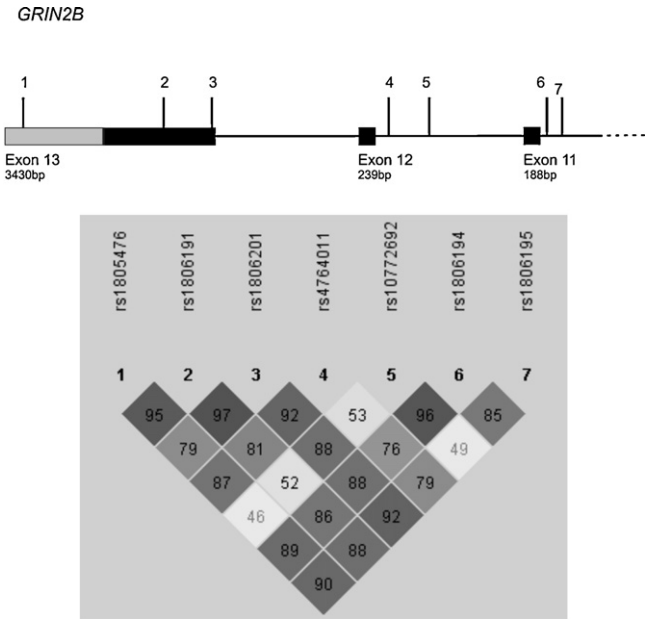


Fig. 2. Graphical representation of single nucleotide polymorphisms (SNP) in relation to the exon–intron organization and Haploview linkage disequilibrium (LD) structure of the 3′ part of the *GRIN2B* gene. Haploview plot showing pairwise LD (D' values) for the seven most frequent SNPs (minor allele frequency >0.250) based on genotypes of 424 individuals in this study. Each square plots the level of LD between a pair of SNPs; comparisons between neighbouring SNPs are arranged in the first line under the names of the SNPs. Scheme is based on D' and LOD score values: dark-grey, strong linkage ($D' = 1$; LOD > 2) grey and light-grey, considerable linkage ($D' < 1$; LOD > 2); white, low linkage. ($D' < 1$; LOD < 2). Numbers in squares are D' values. The numbered vertical lines indicate positions of the SNP in the gene.

3.2. Handedness

The results of the statistical analyses for LQs and absolute handedness for the different *GRIN2B* SNPs are depicted in Table 2.

The LQ effect reached significance for the rs4764011 SNP. The homozygous AA group ($n = 121$, 80.72 ± 3.53) had a higher average LQ than the AG/GG group ($n = 303$, 69.40 ± 3.00; $t_{(422)} = 2.15$; $p = 0.015$). This effect was also reflected by a non-significant trend towards more frequent left-handedness in the AG/GG group (10.85% LHs and 89.15% RHs) as compared to the AA group (5% LHs and 95% RHs; $\chi^2 = 3.53$; $p = 0.06$). Under the co-dominant model, when all three genotype-groups were analyzed separately (see Fig. 3), the LQ effect also reached significance ($F_{(2,421)} = 3.45$; $p < 0.05$; $\eta^2 = 0.02$). Bonferroni-corrected post hoc tests revealed a

Author's personal copy

Table 2
Results of the Edinburgh handedness inventory for the different *GRIN2B* SNPs.

dB SNP rs number	LQ	Absolute handedness
rs1805476	$t_{(406)} = -0.28$; $p = 0.78$	$\chi^2 = 0.04$; $p = 0.87$
rs1805503	$t_{(422)} = 1.31$; $p = 0.21$	$\chi^2 = 2.59$; $p = 0.13$
rs1805247	$t_{(137)} = 1.31$; p = 0.20	$\chi^2 = 2.74$; $p = 0.11$
rs1806191	$t_{(422)} = 0.56$; $p = 0.56$	$\chi^2 = 0.05$; $p = 1.00$
rs1806201	$t_{(422)} = 0.25$; $p = 0.80$	$\chi^2 = 0.17$; $p = 0.74$
rs3026159	$t_{(336)} = 0.26$; $p = 0.80$	$\chi^2 = 0.10$; $p = 0.82$
rs3026160	$t_{(286)} = -0.31$; $p = 0.76$	$\chi^2 = 0.03$; $p = 0.79$
rs4764011	$t_{(422)} = 2.15$; $p = 0.015$	$\chi^2 = 3.53$; $p = 0.06$
rs10772692	$t_{(418)} = -1.61$; $p = 0.11$	$\chi^2 = 1.16$; $p = 0.35$
rs16909222	$t_{(344)} = -0.33$; $p = 0.74$	$\chi^2 = 0.13$; $p = 0.81$
rs1806194	$t_{(414)} = 1.34$; $p = 0.16$	$\chi^2 = 0.70$; $p = 0.48$
rs1806195	$t_{(415)} = 1.27$; $p = 0.20$	$\chi^2 = 0.99$; $p = 0.36$
rs3026164	$t_{(420)} = 0.25$; $p = 0.80$	$\chi^2 = 0.36$; $p = 0.67$
rs1806213	$t_{(422)} = -0.15$; $p = 0.89$	$\chi^2 = 0.34$; $p = 0.67$

significant difference between the GG and AA genotypes ($p < 0.05$), but not between the GG and the AG or the AA and the AG genotype (both p's > 0.43). Yet, the results for rs4764011 should be interpreted with caution, because this SNP did not conform to HWE in our cohort, indicating a statistically significant difference between the observed and expected genotypes in the cohort ($p = 0.002$). Yet, the possibility of genotyping errors for this polymorphism was excluded.

4. Discussion

The aim of the present study was to investigate the influence of *GRIN2B* sequence variations on language lateralization and handedness. In line with several previous studies [36,37], we observed a clear right ear advantage in the DLT, indicating left-hemispheric language dominance. The extent of this asymmetry was modulated by genetic variation within *GRIN2B*, since we found a highly significant association of the synonymous rs1806201 variation in exon 13 with language lateralization. Individuals carrying the homozygous CC genotype exhibited reduced left-hemispheric language dominance as compared to individuals with at least one T allele. Interestingly, this effect was even more pronounced when comparing heterozygous *vs.* homozygous rs1806201 genotypes. This effect was not influenced by a speed accuracy trade-off, since we did not observe an interaction between genotype and side for reaction times. The rs1806201 polymorphism is a synonymous SNP in exon 13 of *GRIN2B* that has been associated with variations in different pathogenetic processes. Huntington's disease patients homozygous for the CC genotype have been found to have a later age of disease onset than patients with the other two genotypes

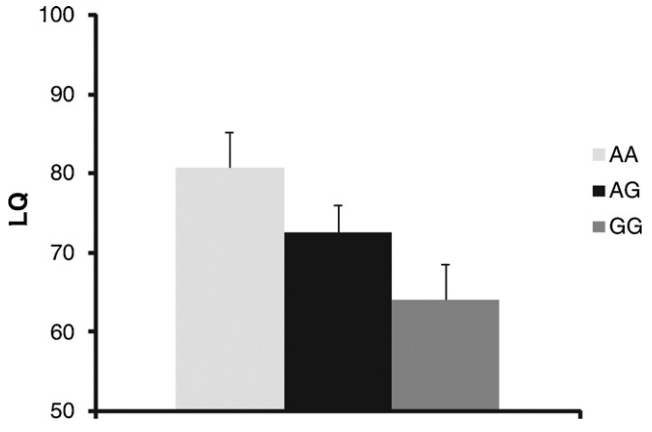


Fig. 3. Association of rs4764011 genotypes and handedness LQ. Error bars show standard error.

[38,39]. Moreover, rs1806201 has been the subject of schizophrenia association studies, but these analyses have produced somewhat inconsistent results [40]. Two studies reported a consistent association of rs1806201 genotypes with individual response to clozapine in schizophrenic patients [41,42].

The finding that rs1806201 C/T heterozygotes exhibited the most pronounced difference between right- and left-ear responses hints at possible heterozygosity effects between *GRIN2B* genotypes and language lateralization. Yet, the small number of the rs1806201 TT homozygous probands prevents firm conclusions regarding this group, meaning that we cannot rule out the alternative hypothesis of a dominant effect of the rare T allele.

Interestingly, there was no association of the rs1806201 polymorphism with handedness. The association with rs4764011 genotypes in this context must be interpreted with caution due to the observed deviation from HWE. Yet, by estimating the LD among the SNPs (Fig. 2) and the moderate sample size of this study, we cannot completely exclude a common genetic effect of *GRIN2B* variation on language lateralization and handedness. Therefore, replication in an independent and larger cohort including a larger number of left-handers appears necessary before sound interpretations can be made.

The association of the 1806201 polymorphism with both schizophrenia and language lateralization suggests that *GRIN2B* is an interesting candidate gene to further investigate the genetic base of atypical language lateralization in schizophrenia [29,30]. Although the potential functional role of the associated SNP remains elusive, our results nevertheless yield further support to the suggestion that glutamatergic neurotransmission and especially the NMDA receptor group is of importance for language lateralization [20,21]. This finding is in line with an earlier study by Hugdahl et al. [19] who found that administration of memantine, a drug that reduces the action of glutamate at the NMDA receptor, leads to reduced language lateralization as tested with the dichotic listening task. According to the structural theory of Kimura [43], during dichotic listening the input to the left ear is not further processed in the right hemisphere but has to be transferred over the corpus callosum in order to be processed in the left temporal lobe [43–45]. Indeed, a recent event related potential study based on trial-by-trial analyses provided strong support for this interpretation [37]. Transmission over the corpus callosum is nearly exclusively based on glutamatergic transmission and activates a mixture of dendritic non-NMDA and NMDA-receptors in the contralateral hemisphere [46]. Thus, variations in NMDA receptor efficacy could modulate interhemispheric transfer via the corpus callosum. Since interhemispheric communication via the corpus callosum is of critical relevance for hemispheric lateralization, it is possible that variations in NMDA receptor efficacy modulate the efficacy of interhemispheric transmission, which in turn influences language lateralization measured with the DLT [47–51].

Interestingly, the corpus callosum has been shown to serve excitatory but also inhibitory influences during dichotic listening [52]. The combined CT/TT group that showed a more pronounced language lateralization in the present study has also been found to show stronger response inhibition processes in comparison to the CC genotype group, as reflected by larger Nogo-N2 and less false alarms in a Go/Nogo paradigm [25]. Thus, these findings suggest that variation in *GRIN2B* might especially be relevant for inhibitory processes mediated via the corpus callosum during dichotic listening, but clearly more research is needed before this theory could be validated. Moreover, a recent study found that women with a CC allele in the rs1806201 SNP made less use of a win–stay strategy in the Iowa gambling task and demonstrated more exploratory behavior during task execution, indicating a relevance of *GRIN2B* for decision making processes [26]. These studies suggest that *GRIN2B* might particularly relevant for frontally mediated executive

Author's personal copy

functions. This assumption is however contradicted by the finding of the present study that variation in *GRIN2B* is not related to performance in verbal intelligence, fluid intelligence and executive functioning measured with the trail-making test, indicating more task-specific effects of variation in *GRIN2B*.

The present study is the first one to report a significant association between a sequence variation and a behavioral measure of language lateralization. Altogether, *GRIN2B* variation explains 2% of the variance in language lateralization, thus supporting the assumption that it is a complex phenotype with a multifactorial background that includes heterogeneous genetic influences. In order to identify other genes that are associated with language lateralization future studies should recruit larger cohorts in order to allow for more comprehensive analyses of different genes and potential epistatic interactions between these.

Another suggestion for future studies comes from the finding that functional hemispheric asymmetries for speech comprehension and production can be dissociated in some individuals [53]. The DLT is a measure of hemispheric asymmetries for phonological speech comprehension that is related to hemodynamic responses in temporal speech regions as well as in frontal areas [15]. Thus, it would be interesting to also investigate a possible relationship between variation in *GRIN2B* and the motor aspects of language lateralization, e.g. by using a word generation task. Additionally, replication in independent healthy samples and especially in cohorts that have been associated with altered lateralization patterns such as schizophrenic [19] or dyslexic patients [54] would be of interest to validate the present results. Finally, such approaches may yield insights to further disentangle the complex interrelation of handedness, language lateralization and psychopathology.

Acknowledgement

This research was supported by a Cutting-Edge Grant from the Ruhr-University of Bochum.

References

[1] Concha ML, Wilson SW. Asymmetry in the epithalamus of vertebrates. J Anat 2001;199:63–84.
[2] George I. Hemispheric asymmetry of songbirds. In: Hughdahl K, Westerhausen R, editors. The two halves of the brain. Cambridge: The MIT Press; 2010. p. 91–120.
[3] Hugdahl K. Lateralization of cognitive processes in the brain. Acta Psychol 2000;105:211–35.
[4] Corballis MC. The evolution and genetics of cerebral asymmetry. Philos Trans R Soc B 2009;364:867–79.
[5] Bethmann A, Tempelmann C, De Bleser R, Scheich H, Brechmann A. Determining language laterality by fMRI and dichotic listening. Brain Res 2007;1133:145–57.
[6] Flöel A, Buyx A, Breitenstein C, Lohmann H, Knecht S. Hemispheric lateralization of spatial attention in right- and left-hemispheric language dominance. Behav Brain Res 2005;158:269–75.
[7] Annett M. Handedness and brain asymmetry: the right shift theory. Hove: Psychology Press; 2002.
[8] McManus IC. Right hand, left hand. London: Orion Books Ltd.; 2002.
[9] Lux S, Keller S, Mackay C, Ebers G, Marshall JC, Cherkas L, et al. Crossed cerebral lateralization for verbal and visuo-spatial function in a pair of handedness discordant monozygotic twins: MRI and fMRI brain imaging. J Anat 2008;212:235–48.
[10] Medland SE, Duffy DL, Wright MJ, Geffen GM, Hay DA, Levy F, et al. Genetic influences on handedness: data from 25,732 Australian and Dutch twin families. Neuropsychologia 2009;47:330–7.
[11] Tzourio-Mazoyer N, Simon G, Crivello F, Jobard G, Zago L, Perchey G, et al. Effect of familial sinistrality on planum temporale surface and brain tissue asymmetries. Cereb Cortex 2010;20:1476–85.
[12] Tervaniemi M, Hugdahl K. Lateralization of auditory–cortex functions. Brain Res Brain Res Rev 2003;43:231–46.
[13] Hugdahl K, Carlsson G, Uvebrant P, Lundervold AJ. Dichotic-listening performance and intracarotid injections of amobarbital in children and adolescents. Preoperative and postoperative comparisons. Arch Neurol 1997;54:1494–500.
[14] Brancucci A. Electroencephalographic and magnetoencephalographic indices of hemispheric asymmetry. In: Hughdahl K, Westerhausen R, editors. The two halves of the brain. Cambridge: The MIT Press; 2010. p. 211–50.
[15] Jäncke L, Shah NJ. Does dichotic listening probe temporal lobe functions? Neurology 2002;58:736–43.
[16] Jäncke L, Buchanan TW, Lutz K, Shah NJ. Focused and nonfocused attention in verbal and emotional dichotic listening: an fMRI study. Brain Lang 2001;78:349–63.
[17] Della Penna S, Brancucci A, Babiloni C, Franciotti R, Pizzella V, Rossi D, et al. Lateralization of dichotic speech stimuli is based on specific auditory pathway interactions: neuromagnetic evidence. Cereb Cortex 2006;17:2303–11.
[18] Sandmann P, Eichele T, Specht K, Jäncke L, Rimol LM, Nordby H, et al. Hemispheric asymmetries in the processing of temporal acoustic cues in consonant–vowel syllables. Restor Neurol Neurosci 2007;25:227–40.
[19] Hugdahl K, Løberg EM, Specht K, Steen VM, van Wageningen H, Jørgensen HA. Auditory hallucinations in schizophrenia: the role of cognitive, brain structural and genetic disturbances in the left temporal lobe. Front Hum Neurosci 2008;1:1–10.
[20] Van Wageningen H, Jørgensen HA, Specht K, Hugdahl K. Evidence for glutamatergic neurotransmission in cognitive control in an auditory attention task. Neurosci Lett 2009;454:171–5.
[21] Van Wageningen H, Jørgensen HA, Specht K, Hugdahl K. A 1H-MR spectroscopy study of changes in glutamate and glutamine (Glx) concentrations in frontal spectra after administration of memantine. Cereb Cortex 2010;20:798–803.
[22] Loftis JM, Janowsky A. The N-methyl-D-aspartate receptor subunit NR2B: localization, functional properties, regulation, and chemical implications. Pharmacol Ther 2003;97:55–85.
[23] Villmann C, Becker CM. On the hypes and falls in neuroprotection: targeting the NMDA receptor. Neuroscientist 2007;13:594–615.
[24] Tang YP, Shimizu E, Dube GR, Rampon C, Kerchner GA, Zhuo M, et al. Genetic enhancement of learning and memory in mice. Nature 1999;401:63–9.
[25] Beste C, Baune BT, Domschke K, Falkenstein M, Konrad C. Dissociable influences of NR2B-receptor related neural transmission on functions of distinct associative basal ganglia circuits. Neuroimage 2010;52:309–15.
[26] Ness V, Arning L, Niesert HE, Stüttgen MC, Epplen JT, Beste C. Variations in the GRIN2B gene are associated with risky decision-making. Neuropharmacology 2011, doi:10.1016/j.neuropharm.2011.06.023 [Epub ahead of print].
[27] Cherlyn SYT, Woon PS, Liu JJ, Ong WY, Tsai GC, Sim K. Genetic association studies of glutamate, GABA and related genes in schizophrenia and bipolar disorder: a decade of advance. Neurosci Biobehav Rev 2010;34:958–77.
[28] Quin S, Zhao X, Pan Y, Liu J, Feng G, Fu J, et al. An association study of the N-methyl-D-aspartate receptor NR1 subunit gene (GRIN1) and NR2B subunit gene (GRIN2B) in schizophrenia with universal DNA microarray. Eur J Hum Genet 2005;13:807–14.
[29] Collinson SL, Mackay CE, Jiaqing O, James ACD, Crow TJ. Dichotic listening impairments in early onset schizophrenia are associated with reduced left temporal lobe volume. Schizophr Res 2009;112:24–31.
[30] Løberg EM, Jørgensen HA, Hugdahl K. Dichotic listening in schizophrenic patients: effects of previous vs. ongoing auditory hallucinations. Psychiatry Res 2004;128:167–74.
[31] Lehrl S. Mehrfachwahl–Wortschatz–Intelligenztest MWT-B. Balingen: Spitta Verlag; 2005.
[32] Horn W. L–P–S Leistungsprüfsystem. Göttingen: Hogrefe; 1983.
[33] Arbuthnott K, Frank J. Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. J Clin Exp Neuropsychol 2000;22:518–28.
[34] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97–113.
[35] Stephens M, Scheet P. Accounting for decay of linkage disequilibrium in haplotype inference and missing-data imputation. Am J Hum Genet 2005;76:449–62.
[36] Hugdahl K. Dichotic listening in the study of auditory laterality. In: Hughdahl K, Davidson RJ, editors. The asymmetrical brain. Cambridge: The MIT Press; 2005. p. 441–76.
[37] Bayazit O, Öniz A, Hahn C, Güntürkün O, Özgören M. Dichotic listening revisited: trial-by-trial ERP analyses reveal intra- and interhemispheric differences. Neuropsychologia 2009;47:536–45.
[38] Arning L, Saft C, Wieczorek S, Andrich J, Kraus PH, Epplen JT. NR2A and NR2B gene variations modify age at onset in Huntington's disease in a sex-specific manner. Hum Genet 2007;122:175–82.
[39] Arning L, Kraus PH, Valentin S, Saft C, Andrich J, Epplen JT. NR2A and NR2B receptor gene variations modify age at onset in Huntington's disease. Neurogenetics 2005;6:25–8.
[40] Li D, He L. Association study between the NMDA receptor 2B subunit gene (GRIN2B) and schizophrenia: a HuGE review and meta-analysis. Genet Med 2007;9:4–8.
[41] Hong CJ, Yu YW, Lin CH, Cheng CY, Tsai SJ. Association analysis for NMDA receptor subunit 2B (GRIN2B) genetic variants and psychopathology and clozapine response in schizophrenia. Psychiatr Genet 2001;11:219–22.
[42] Chiu HJ, Wang YC, Liou YJ, Lai IC, Chen JY. Association analysis of the genetic variants of the N-methyl D-aspartate receptor subunit 2b (NR2b) and treatment-refractory schizophrenia in the Chinese. Neuropsychobiology 2003;47:178–81.
[43] Kimura D. Cerebral dominance and the perception of verbal stimuli. Can J Psychol 1961;15:156–65.
[44] Pollmann S, Lepsien J, Hugdahl K, von Cramon YD. Auditory target detection in dichotic listening involves the orbitofrontal and hippocampal paralimbic belts. Cereb Cortex 2004;14:903–13.

Author's personal copy

[45] O'Leary DS. Effects of attention on hemispheric asymmetry. In: Hughdahl K, Davidson RJ, editors. The asymmetrical brain. Cambridge: The MIT Press; 2005. p. 477–509.
[46] Kumar SS, Huguenard JR. Properties of exitatory synaptic connections mediated by the corpus callosum in the developing rat neocortex. J Neurophysiol 2001;86:2973–85.
[47] Hausmann M, Güntürkün O. Steroid fluctuations modify functional cerebral asymmetries: the hypothesis of progesterone-mediated interhemispheric decoupling. Neuropsychologia 2000;38:1362–74.
[48] Bayer U, Kessler N, Güntürkün O, Hausmann M. Interhemispheric interaction during the menstrual cycle. Neuropsychologia 2008;46:2415–22.
[49] Westerhausen R, Hugdahl K. The corpus callosum in dichotic listening studies of hemispheric asymmetry: a review of clinical and experimental evidence. Neurosci Biobehav Rev 2008;32:1044–54.
[50] Josse G, Seghier ML, Kherif F, Price CJ. Explaning function with anatomy: language lateralization and corpus callosom size. J Neurosci 2008;28: 14132–9.
[51] Nowicka A, Tacikowski P. Transcallosal transfer of information and functional asymmetry of the human brain. Laterality 2011;16:35–74.
[52] Gadea M, Marti-Bonmatí L, Arana E, Espert R, Salvador A, Casanova B. Corpus callosum function in verbal dichotic listening: inferences from a longitudinal follow-up of relapsing-remitting multiple sclerosis patients. Brain Lang 2009;110:101–5.
[53] Tzourio-Mazoyer N, Josse G, Crivello F, Mazoyer B. Interindividual variability in the hemispheric organization for speech. Neuroimage 2004;21: 422–35.
[54] Annett M, Kilshaw D. Lateral preference and skill in dyslexics: implications of the right shift theory. J Child Psychol Psychiatry 1984;25:357–77.