

Cognitive Control Processes and Functional Cerebral Asymmetries: Association with Variation in the Handedness-Associated Gene *LRRTM1*

Christian Beste^{1,2} · Larissa Arning³ · Wanda M. Gerding³ · Jörg T. Epplen³ · Alexandra Mertins⁴ · Melanie C. Röder⁴ · Josef J. Bless⁵ · Kenneth Hugdahl^{5,6,8} · René Westerhausen⁷ · Onur Güntürkün⁴ · Sebastian Ocklenburg⁴

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Abstract Cognitive control processes play an essential role not only in controlling actions but also in guiding attentional selection processes. Interestingly, these processes are strongly affected by organizational principles of the cerebral cortex and related functional asymmetries, but the neurobiological foundations are elusive. We ask whether neurobiological mechanisms that affect functional cerebral asymmetries will also modulate effects of top-down control processes on functional cerebral asymmetries. To this end, we examined potential effects of the imprinted gene leucine-rich repeat transmembrane neuronal 1 (*LRRTM1*) on attentional biasing processes in a forced attention dichotic listening task in 983 healthy adult participants of Caucasian descent using the “iDichotic smartphone app.” The results show that functional cerebral

asymmetries in the language domain are associated with the rs6733871 *LRRTM1* polymorphism when cognitive control and top-down attentional mechanisms modulate processes in bottom-up attentional selection processes that are dependent on functional cerebral asymmetries. There is no evidence for an effect of *LRRTM1* on functional cerebral asymmetries in the language domain unrelated to cognitive control processes. The results suggest that cognitive control processes are an important factor to consider when being interested in the molecular genetic basis of functional cerebral architecture.

Keywords Cognitive control · Dichotic listening · Cerebral asymmetries · *LRRTM1* · Genetics · Smartphone

✉ Christian Beste
christian.beste@uniklinikum-dresden.de

¹ Cognitive Neurophysiology, Department of Child and Adolescent Psychiatry, Faculty of Medicine, TU Dresden, Schubertstrasse 42, 01309 Dresden, Germany

² Experimental Neurobiology, National Institute of Mental Health, Klecany, Czech Republic

³ Department of Human Genetics, Ruhr-University Bochum, Bochum, Germany

⁴ Institute of Cognitive Neuroscience, Biopsychology, Department of Psychology, Ruhr-University Bochum, Bochum, Germany

⁵ Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway

⁶ NORMENT Center of Excellence, University of Oslo, Oslo, Norway

⁷ Department of Psychology, University of Oslo, Oslo, Norway

⁸ Department of Psychiatry, Haukeklund University Hospital, Bergen, Norway

Introduction

Cognitive control processes play an essential role not only in controlling actions [1] but also in guiding attentional selection processes [2, 3]. It has been suggested that various perceptual features of incoming information compete with each other to gain control over behavior. Whether one feature wins the competition and controls behavior depends on the relative saliency and intentional biases favoring one over the other features [2–6]. Such processes can, for example, be observed in the “cocktail party phenomenon” [7]. Interestingly, these processes are strongly affected by organizational principles of the cerebral cortex and related functional asymmetries in information processing [8–10].

An experimental paradigm that has been frequently used to behaviorally assess the interaction of lateralized bottom-up-driven perceptual processing and top-down cognitive control processes is the forced attention dichotic listening paradigm. This paradigm has originally been described by Bryden et al.

and Hugdahl and Andersson [11, 12] and later validated using functional neuroimaging [10]. In the forced attention dichotic listening task, participants are tested in three conditions: a non-forced condition in which participants are instructed to report the syllable they heard best, a forced-right (FR) condition in which they are instructed to concentrate only on the syllables presented to the right ear, and a forced-left (FL) condition in which participants are instructed to attend only to the syllables presented to the left ear [13]. A well-replicated finding is that in the non-forced condition, a large majority of participants report the stimulus presented to the right more often than the stimulus presented to the left ear, and that the right ear advantage is usually further enhanced in the FR condition, but diminished in the FL condition [10, 12]. The findings from the non-forced condition implicate that processes attributable to concepts like saliency and bottom-up attentional mechanisms [2, 3] are closely inter-related with neurobiological mechanisms determining functional cerebral asymmetries. This has until now not been investigated in detail even though some studies exist suggesting this [14, 15]. However, even more important is that these bottom-up functional cerebral asymmetries can be modulated by top-down attentional selection and cognitive control [9, 10, 13, 16, 17], e.g., as suggested by the results in the FL and FR conditions.

The neurobiological foundations related to top-down attentional control-dependent modulation of functional cerebral asymmetries are yet elusive. Interestingly, even though FR and FL conditions require top-down attentional control, FL conditions require stronger attentional control [10, 18] suggesting that the amount of cognitive control needed is a direct function of the underlying functional cerebral asymmetry. It is possible that top-down attentional control processes are affected by mechanisms determining processing in the bottom-up channel, i.e., functional cerebral asymmetries. The question is if neurobiological mechanisms that affect functional cerebral asymmetries will also modulate effects of top-down control processes on functional cerebral asymmetries?

In the current study, we examine this question by examining the potential effects of a polymorphism of the imprinted gene leucine-rich repeat transmembrane neuronal 1 (*LRRTM1*) located at chromosome 2p12 on attentional biasing processes in a forced attention dichotic listening task implemented in the iDichotic smartphone app [19, 20]. The antisense-oriented leucine-rich repeat transmembrane (*LRRTM*) 1 gene is located within *CTNNA2* which contains an alternative bidirectional promoter that is used for the transcription of both genes, *CTNNA2* and *LRRTM1* [21]. We choose to investigate *LRRTM1* because variation in this gene has been shown to be associated with handedness, a form of hemispheric asymmetry strongly correlated with language lateralization [22]. Interestingly, the same haplotype associated with handedness has been found to be over-transmitted paternally in schizophrenic patients [22]. A possible nexus of

LRRTM1 and schizophrenia has also been reported by [23] who found the minor allele of the *LRRTM1* rs6733871 SNP to be significantly maternally under-transmitted to schizophrenic patients [23]. This is relevant for the current study on *LRRTM1* as dichotic listening task performance and related functional cerebral asymmetries are typically reduced in schizophrenia [24]. Moreover, patients with schizophrenia show problems to attend to and report FL stimuli in the DL task [25–27]. While these effects can also well be an effect of alterations in various neurotransmitter systems altered in schizophrenia (e.g., dopamine, glutamate) and of relevance for top-down attentional control [28], it cannot be excluded that factors associated with changes in cerebral architecture in schizophrenia (i.e., *LRRTM1*) are relevant for changes in functional cerebral asymmetries as well. If this is the case, it is likely that *LRRTM1* may affect attentional biases in the DL task also in healthy subjects. Based on the data of Ludwig et al. [23], we specifically focused on the non-synonymous *LRRTM1* SNP rs6733871 that leads to a substitution of asparagine with serine. We assessed whether it was associated with differential effects in forced attention dichotic listening.

Experimental Procedures

Participants

Overall, 983 genetically unrelated, healthy adult participants of Caucasian descent for at least two generations participated in the present study (678 women and 305 men). Mean age was 24.66 ± 6.64 years. None of the participants had a history of any neurological or psychiatric diseases and all of them were native German speakers. No participants were included in the cohort that had been forced to write with the right hand in school, although they actually would have preferred to use the left. Before testing, all prospective participants were instructed to take a simple hearing test administered within the iDichotic app [19, 20]. In this pretest, participants listened to a continuous pure tone of 1000 Hz. They were asked to reduce the sound level by sliding a bar on the iPod touch display to the left until they were not longer able to hear the sound. Only participants with normal hearing capabilities and no more than 20% hearing difference between the ears were included in final sample. 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.

Testing Protocol

Participants were tested in standard laboratory testing rooms. First, the aim of the study was explained and participants signed the informed consent form. Then oral mucosa samples

for genotyping (see next section) were collected using oral swabs.

Subsequently, the Edinburgh Handedness Inventory (EHI) [29] was used to assess handedness. This questionnaire consists of ten items. Based on the participants answer, a laterality quotient can be calculated that indicated the individual strength and direction of handedness from consistent left-handedness (−100) to consistent right-handedness (+100). Dichotic listening performance was assessed using the iDichotic app for iOS [19, 20]. This app is available free of charge in the Apple app store and can be used with any iOS device (iPhone, iPad, iPod touch). In the present study, testing was performed using an iPod touch (Apple Inc., Cupertino, CA) and over-the-ear headphones outfitted with disposable hygienic sleeves. Stimuli were based on the standard Bergen dichotic listening paradigm [26] and consisted of six consonant-vowel syllables (BA, DA, GA, KA, PA, TA) presented simultaneously in pairs. This resulted in a total of 36 pairs, 30 dichotic stimulus pairs (e.g., BA-DA) and 6 homonym stimulus pairs (e.g., BA-BA). Stimuli were spoken by a male German speaker with constant intensity and intonation. Stimulus duration was between 400 and 500 ms, with an inter-stimulus interval of 4000 ms. Within stimulus pairs, onsets of the initial stop-consonants were temporally aligned to each other. Overall, there were three different experimental conditions. First, the classic non-forced (NF) condition (called “Listen” in the app) was presented. Here, participants were instructed to report the syllable heard best. In the forced-left (FL) condition (called “Concentrate Left” in the app), participants were instructed to only concentrate on the left ear and report the syllable they heard on that ear. In contrast, in the forced-right (FR) condition (called “Concentrate Right” in the app), participants were instructed to only concentrate on the right ear and report the syllable they heard on that ear. Participants were instructed to report which stimulus they heard best by touching one out of six syllables on the touchscreen of the mobile device. For every participant and condition, the order in which the six syllables appeared on the reaction screen was randomized.

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). Genotyping the non-synonymous *LRRTM1* SNP rs6733871 (N330S) was conducted by polymerase chain reaction (PCR) and differential enzymatic analysis with the PCR restriction fragment length polymorphism (RFLP) method. The presence of cytosine at the SNP position results in the presence of a *DdeI* restriction site that is absent in the presence of the thymine allele. A 352-bp length fragment containing the SNP was amplified by PCR using the

oligonucleotides: forward = 5'-CAGGTGGCCGCTGGTG-3' and reverse = 5'-CCTGGAGAAAATGGACTTGTGCG-3'. The PCR product is then digested with *DdeI*, yielding fragments in sizes unique to each *LRRTM1* rs6733871 genotype. The fragments can be visualized on 3% agarose gels. Oligonucleotides were designed using Primer Express 2.0 Software (Applied Biosystems). Based on the individual allelic configuration for the non-synonymous *LRRTM1* SNP rs6733871, each participant was grouped into one of three possible groups (TT, TC, or CC genotype).

Results

Handedness

The average handedness laterality quotient (LQ) was 72.00 ± 45.89 (range −100 to +100). To investigate the effect of *LRRTM1* rs6733871 on handedness, we analyzed the EHI LQ using univariate ANOVA with *LRRTM1* genotype (TT, TC, CC) as a fixed factor. However, the effect failed to reach significance ($F_{(1,980)} = 1.50$; $p = 0.22$). Additionally, we investigated handedness direction (left-handed, right-handed) and handedness consistency groups (consistent left-handed, left-handed, ambidexterity with a tendency towards left-handedness, ambidexterity with a tendency towards right-handedness, right-handed, consistent right-handed) using non-parametric Kruskal-Wallis H tests. While the effect for handedness direction failed to reach significance ($p = 0.50$), the effect for handedness groups only narrowly missed significance ($p = 0.085$).

Dichotic Listening: Perceptual Laterality

To investigate the effect of *LRRTM1* rs6733871 on language lateralization (see Fig. 1), we analyzed correct responses in the non-forced condition using a 2×3 repeated measures ANOVA with the between-subjects factor *LRRTM1* genotype (TT, TC, CC) and the within-subjects factor ear (left ear, right ear). The main effect of ear reached significance ($F_{(1,980)} = 52.10$; $p < 0.001$; partial $\eta^2 = 0.05$), indicating that participants more often reported the syllable they heard on the right ear (12.12 ± 0.21) than the syllable they heard on the left ear (9.55 ± 1.86). Both the main effect of *LRRTM1* genotype ($F_{(1,980)} = 0.51$; $p = 0.60$) and the *LRRTM1* genotype \times ear interaction ($F_{(2,980)} = 0.77$; $p = 0.46$) failed to reach significance.

Dichotic Listening: Cognitive Control

To investigate the effect of *LRRTM1* rs6733871 on cognitive control, we analyzed correct responses in the two forced conditions using a $2 \times 2 \times 3$ repeated measures ANOVA with the

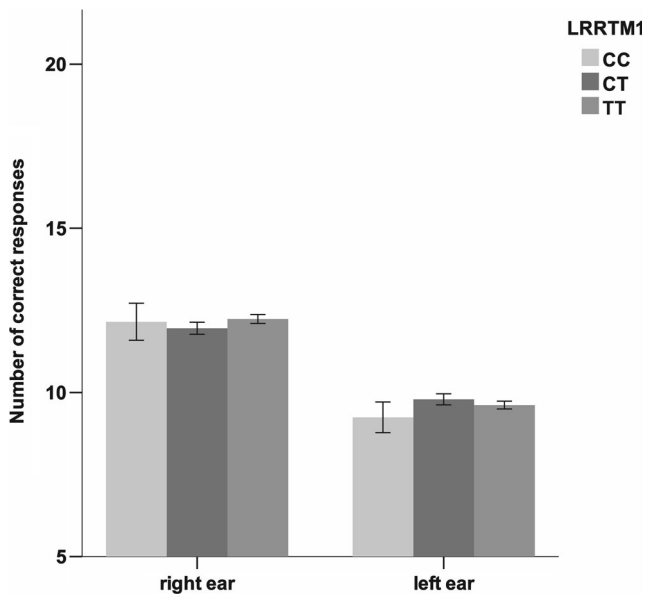


Fig. 1 Right ear and left ear responses in the non-forced condition of the dichotic listening task in relation to *LRRTM1* genotype

between-subjects factor *LRRTM1* genotype (TT, TC, CC) and the within-subjects factors condition (forced left, forced right) and ear (left ear, right ear). Both the main effects of condition ($F_{(1,980)} = 70.86$; $p < 0.001$; partial $\eta^2 = 0.07$) and ear ($F_{(1,980)} = 100.82$; $p < 0.001$; partial $\eta^2 = 0.09$), as well as the interaction condition \times ear ($F_{(1,980)} = 225.10$; $p < 0.001$; partial $\eta^2 = 0.19$), reached significance. This interaction indicated that on average, participants showed a right ear advantage in the forced right condition (right ear 15.81 ± 0.26 ; left ear 7.73 ± 0.21 ; Bonferroni-corrected post hoc test $p < 0.001$) and a left ear advantage in the forced left condition (right ear 9.59 ± 0.24 ; left ear 12.15 ± 0.27 ; Bonferroni-corrected post hoc test $p < 0.001$). Importantly, the ear effect was modulated by *LRRTM1* genotype, as indicated by a significant *LRRTM1* genotype \times ear interaction ($F_{(2,980)} = 5.64$; $p < 0.005$; partial $\eta^2 = 0.01$). On average, participants with the rare CC genotype had a numerically larger asymmetry between left and right ear responses (right ear 13.42 ± 4.60 ; left ear 9.24 ± 4.40 ; difference 4.18; Bonferroni-corrected post hoc test $p < 0.001$) then those with the CT (right ear 12.09 ± 0.15 ; left ear 10.37 ± 0.14 ; difference 1.72; Bonferroni-corrected post hoc test $p < 0.001$) and TT genotypes (right ear 12.58 ± 0.10 ; left ear 10.20 ± 0.10 ; difference 2.38; Bonferroni-corrected post hoc test $p < 0.001$). All other main effects and interactions failed to reach significance (all p 's > 0.15).

As this result was difficult to interpret as there was a left ear advantage in the forced left condition and a right ear advantage in the forced right condition, we also calculated two separate ANOVAs for the two conditions. Here, the *LRRTM1* genotype \times ear interaction reached significance for the forced left condition ($F_{(2,980)} = 4.30$; $p < 0.05$; partial $\eta^2 = 0.01$), but missed significance for the forced right condition

($F_{(2,980)} = 2.16$; $p = 0.15$). Thus, the effect of genetic variation in *LRRTM1* within the two cognitive control conditions seems to be driven by the forced left condition (Fig. 2).

Discussion

In the current study, we examined the relevance of the non-synonymous *LRRTM1* SNP rs6733871 for both bottom-up auditory lateralization and top-down cognitive control processes using the forced-attention dichotic listening task [11, 12]. To this end, we used the iDichotic smartphone app [19, 20].

On average, participants showed a right ear advantage in the non-forced condition and FR condition, but a left ear advantage in the FL condition. Thus, we could successfully replicate the typical findings observed in the laboratory version of the forced attention dichotic listening task [10, 12] in our sample of 983 healthy adults. Thus, our data further confirm the conclusion of Bless et al. [19, 20] that smartphone-based data collection is an effective method to test large sample in an efficient and less-consuming, but still reliable way. This is particularly important in large-scale studies on the cognitive genetics of higher cognitive functions. Also, using smartphone-based data collections has huge advantages over traditional laboratory-based data collection when testing population in the field that are difficult to convince to come to the lab.

LRRTM1 had previously been associated with handedness. Francks et al. [22] found a significant association of a *LRRTM1* haplotype with handedness in a sample of dyslexic siblings, when the haplotype was inherited paternally. However, this association could not be found in a healthy

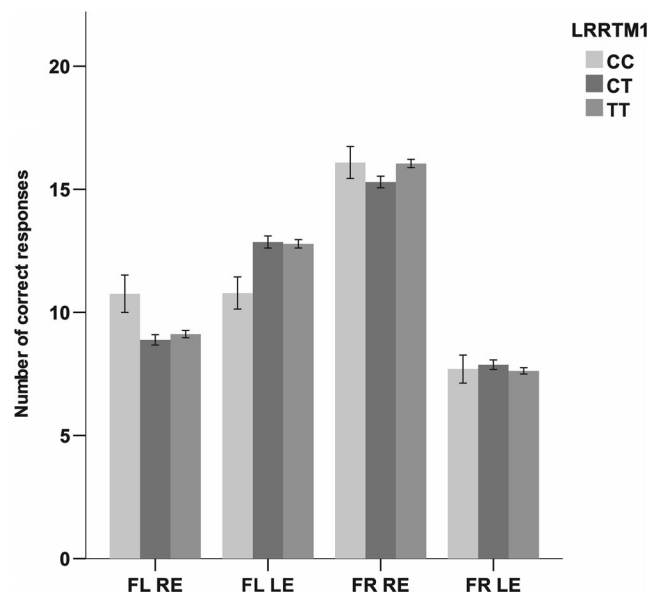


Fig. 2 Right ear (RE) and left ear (LE) responses in the forced-left (FL) and forced-right (FR) conditions of the dichotic listening task in relation to *LRRTM1* genotype

cohort. Replicating these findings of Francks et al. [22] in a sample of 983 healthy adults for the examined *LRRTM1* rs6733871 SNP, we did not find any significant association of genetic variation in *LRRTM1* and handedness LQ and handedness direction. Only the effect for handedness groups came somewhat close to reaching nominal significance ($p = 0.085$). This further supports the idea that *LRRTM1* is related to handedness in clinical groups, but not necessarily in healthy populations.

Handedness is to some extent correlated with language lateralization, and classic monogenic theories about the ontogenesis of the two traits assume that they are determined by the same ontogenetic factors (for an overview see [30]. Thus, it could be assumed that genetic variation in the handedness-associated *LRRTM1* gene could potentially influence language lateralization, e.g., as measured in the non-forced condition of the forced attention dichotic listening task. However, in line with our handedness data, the analyzed *LRRTM1* polymorphism did not show a significant association with performance in the non-forced condition, as no differences between *LRRTM1* rs6733871 genotypes were observed for the number of syllables reported for the left or right ear.

In contrast to the results of the non-forced condition, the results of the two forced conditions revealed a significant interaction of ear and *LRRTM1* genotype. Under forced attention conditions (FL and FR), the group homozygous for the minor C allele revealed an overall larger asymmetry than participants with at least one major T allele. Further analysis revealed that this effect was mainly driven by the forced left condition. It has been argued that forced left and forced right conditions involved different cognitive processes, because in the FR condition, subjects are asked to report the input which is already perceptually “preferred,” while the FL attention situation requires the processing of the weaker stimulus in the presence of a competing and stronger stimulus [10, 31]. The forced left condition therefore requires stronger top-down cognitive control [10, 16, 17, 31]. The current results therefore suggest that the degree of top-down attentional control needed to perform a specific task plays a key role in the observed effects. In particular, under conditions that make it necessary to exert strong top-down attentional control, genetic variation in *LRRTM1* seems to affect cognitive control.

The entire pattern of results therefore shows that functional cerebral asymmetries in the language domain are only affected by *LRRTM1* when cognitive control and hence top-down attentional mechanisms modulate processes in the bottom-up channel that are dependent on functional cerebral asymmetries. This finding further supports the idea of an intricate interrelation of cognitive control and cerebral asymmetries. For example, a recent event-related potential study with lateralized tachistoscopic presentation of verbal “Go” and “Nogo” stimuli found that participants showed a left-hemispheric dominance on the behavioral level [32]. On

the neurophysiological level, the Nogo-N2 was stronger when response inhibition was initiated by stimuli presented in the LVF. This effect was driven by stronger activations in bilateral medial-prefrontal networks, as well as left parietal networks. Thus, hemispheric dominances in early stimulus processing can place differential demands on bilateral cognitive processes like cognitive control. Our results extend these findings as they suggest that *LRRTM1* may play an important role in the ontogenesis of this interrelation.

Our data suggest that the extent of cognitive modulation a participant homozygous for the rs6733871 C allele can exhibit over their performance in the dichotic listening task is lower than that in CT and TT genotypes. This is particularly interesting as Ludwig et al. [23] reported the minor rs6733871 C allele to be significantly maternally under-transmitted to schizophrenic patients. Similar to our data pattern for the CC genotype, Oie and Hugdahl [27] reported that schizophrenic patients also failed to show a left ear advantage in the FL condition, indicating lower cognitive control in patients than in controls. Thus, our data support the idea that *LRRTM1* is a gene associated with higher brain functions not only in psychiatric disorders but also in the healthy population. This suggestion is strongly supported by recent animal research. Takashima et al. [33] created a *Lrrtm1* knockout model in mice and compared the knockouts behaviorally and morphologically to wild-type mice. Morphologically, the knockout mice had a reduced hippocampus size and reduced synaptic density. Behaviorally, they showed reduced locomotor activity, altered behavioral responses to novel environments, and avoidance of approach to large inanimate objects. Moreover, they exhibited deficits in social discrimination and spatial memory. Based on this pattern of results, Takashima et al. [33] concluded that *Lrrtm1* knockout mice showed impaired cognitive functioning, suggesting a role of this gene for higher cognitive functions in non-human mammals as well. While the functional cascade leading to a relation of genetic variation in *LRRTM1* and higher cognitive function is not known at the present time, one particularly interesting recent finding on the functional level is that *LRRTM1* expression influences the expression of brain-enriched alternative transcripts of *CTNNA2* [21]. *CTNNA2* encodes an α -catenin that is involved in regulating cell-cell and cell-matrix interactions. It shares a bidirectional promoter region with *LRRTM1*, and activity of these promoters causes an alternative *CTNNA2* transcript which is expressed in the nervous system [21]. As variation in *CTNNA2* has recently been linked to impulsivity [34], a trait representing low cognitive control over one's actions, this association certainly would be an interesting one to further explore in future studies.

One possible limitation of our study was that we used the EHI to assess handedness. While this questionnaire is the most widely used instrument to assess hand preferences, it has been criticized by some authors, mainly because it has been

suggested that the EHI contains redundant items that might bias measurement [35, 36]. Thus, future studies investigating the role of *LRRTM1* for handedness should also include other means to assess handedness.

Another potential issue is the fact that the app version of the forced attention dichotic listening task seems to yield smaller effect sizes for the key interaction condition \times ear than studies using the traditional laboratory version of this task. We observed a partial $\eta^2 = 0.19$ for this interaction, which is in line with a recent study also using this app in an independent family cohort [37]. In this study, an effect size of partial $\eta^2 = 0.20$ was observed in the age category of the present cohort. However, in a study using the task in the fMRI scanner, Kompus et al. observed an effect size of $\eta^2 = 0.38$ [10]. Thus, the traditional laboratory version of the task seems to yield stronger effects than the app we used. This should be taken into account when planning future studies.

In summary, our results show no evidence for an effect of *LRRTM1* on functional cerebral asymmetries in the language domain unrelated to cognitive control processes. However, our findings suggest that in healthy participants, *LRRTM1* is relevant for cognitive control and top-down attentional mechanisms that modulate processes in bottom-up attentional selection processes that are dependent on functional cerebral asymmetries.

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Compliance with Ethical Standards 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.

Conflict of Interest The authors declare that they have no conflict of interest.

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