



Mirrored brain organization: Statistical anomaly or reversal of hemispheric functional segregation bias?

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Humans demonstrate a prototypical hemispheric functional segregation pattern, with language and praxis lateralizing to the left hemisphere and spatial attention, face recognition, and emotional prosody to the right hemisphere. In this study, we used fMRI to determine laterality for all five functions in each participant. Crucially, we recruited a sample of left-handers preselected for atypical (right) language dominance ($n = 24$), which allowed us to characterize hemispheric asymmetry of the other functions and compare their functional segregation pattern with that of left-handers showing typical language dominance ($n = 39$). Our results revealed that most participants with left language dominance display the prototypical pattern of functional hemispheric segregation (44%) or deviate from this pattern in only one function (35%). Similarly, the vast majority of right language dominant participants demonstrated a completely mirrored brain organization (50%) or a reversal for all but one cognitive function (32%). Participants deviating by more than one function from the standard segregation pattern showed poorer cognitive performance, in line with an oft-presumed biological advantage of hemispheric functional segregation.

hemispheric dominance | functional brain asymmetry | hemispheric segregation | language dominance | lateralization

Many cognitive functions rely more crucially on one hemisphere compared with the other, an instance of neural specialization known as “hemispheric dominance” or “functional lateralization.” Even though it is among the oldest findings in cognitive neuroscience (1), many questions regarding this fundamental property of brain organization remain to be answered (2). For instance, while it is known that hemisphere asymmetries arise early in human ontogenesis and likely result from complex interactions between genetic and nongenetic factors, its exact developmental determinants remain to be elucidated (3). Equally enigmatic is their phylogenetic evolution. The presence of behavioral and brain asymmetries in a wide range of vertebrate and even invertebrate animals (4–7) suggests that lateralization occurred early in evolutionary history (8, 9). However, it still has not been clarified exactly how the brain came to be lateralized and the extent to which the origins of neurobehavioral asymmetry are similar across species (3, 10, 11). What is clear is that functional asymmetry implies a functional segregation within the brain, as some functions wind up dominant in one hemisphere, while dominance for others is established in the opposite hemisphere (2). Hemispheric functional segregation is often presumed to confer selective advantage (12), which is most commonly explained in terms of increasing neural efficiency, for example, by avoiding redundancy, enhancing the brain’s parallel processing capacity, and preventing conflicts between duplicate control systems (13).

Lateralized cognitive functions exhibit strong population-wise directional biases in humans; for example, language is left hemisphere dominant in approximately 84% of the general population (14). Thus, a minority of people deviate from this typical organization pattern, either by having a right hemisphere dominance for language (RLD) or by lacking obvious asymmetry and showing

bilateral representation. Such atypical hemisphere dominance is equally rare in other left hemisphere functions, such as praxis and arithmetic, as well as in right hemisphere functions, such as spatial processing, face recognition, and comprehending emotional prosody (15–21).

From the fact that cognitive functions have directional population-level biases, it follows that hemispheric functional segregation would also exhibit a prototypical directional asymmetry, with most humans displaying a pattern in which language and praxis are dominant in the left hemisphere and spatial attention, prosody, and face recognition are dominant in the right hemisphere. A crucial question that then arises is whether atypical lateralization of one function flags a full reversal of the typical hemispheric functional segregation pattern. Two views in the current literature offer diverging answers to this question. According to the statistical hypothesis, the lateralization of different functions does not influence the other functions, and instead each follows its own directional bias (22). This hypothesis is supported by a host of studies reporting absence of an association between the direction of hemispheric dominance for language and spatial processes (21, 23–27). Moreover, while these functions usually lateralize to opposite hemispheres, in some participants they instead crowd in the same hemisphere with no apparent behavioral consequences. An alternative account of functional segregation is provided by the causal hypothesis, which proposes that functions interact during the establishment of their hemispheric dominance,

Significance

It is commonly assumed that cognitive functions are asymmetrically distributed across the brain according to a stereotypical pattern, with some dominant in the left hemisphere and others dominant in the right hemisphere. While presumed to present a biological optimum, this pattern is based predominantly on studies investigating only one function. We provide insight into human brain variability by determining hemisphere dominance for five functions within the same individuals. First, while typical organization is generally maintained, it is subject to more variation than is often assumed. Second, human brain organization can be completely mirrored. Finally, the finding of poorer cognitive performance in participants who strongly deviate from typical organization or its complete reversal agrees with its postulated selective advantage.

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for example, because the lateralization of one process forces another process to the opposite hemisphere (28, 29), or because homotopic brain regions mutually inhibit each other via the corpus callosum (30). Regardless of the underlying mechanism, the causal hypothesis claims that functions do not lateralize independently of one another.

While the causal hypothesis has difficulty explaining functional crowding, some compelling evidence in favor of this view comes from neuroimaging studies in participants with RLD showing that all or most of them were also atypically lateralized for praxis (31), spatial attention (32), face processing (33), and arithmetic (34). At the same time, these findings argue against the complete independence of functional lateralization, which the statistical hypothesis posits, because independent biases would predict more crowding, not increased atypical laterality.

Given these conflicting findings, whether and if so, to what extent the lateralized asymmetric brain functions are related to one another remain unclear. The present study aimed to shed light on this issue by using fMRI to determine hemispheric dominance while participants generated words (language), pantomimed tool movements (praxis), made line bisection judgments (spatial attention), observed human faces (face recognition), and evaluated the emotional intonation of speech (emotional prosody). Crucially, besides including participants with typical left hemisphere dominance for language (LLD), we enriched our sample with individuals with RLD, as the causal and statistical hypotheses make strongly divergent predictions about their hemisphere functional segregation patterns. If causal mechanisms underlie lateralization, then all participants with RLD will show a complete hemisphere reversal of their cognitive functions. The statistical hypothesis, in contrast, predicts that most individuals with RLD otherwise will be typically lateralized. Note that both hypotheses predict that most (statistical hypothesis) or all (causal hypothesis) LLD participants will demonstrate a typical pattern of hemispheric functional segregation.

To ensure that we could include a sizeable sample of RLD participants in a cost-efficient way, we used a behavioral visual half-field task to identify individuals likely to be RLD and subsequently invited them to participate in a follow-up MRI session. The visual half-field task has previously been shown to reliably predict fMRI-based language dominance (35). During this task, participants were instructed to name written words presented either on the left or right side of the screen as quickly as possible. As visual stimuli are projected to the contralateral visual cortex, faster and more accurate responses on words in the right visual field indicate LLD, while a relative advantage for stimuli in the left visual field indicate RLD. All participants with suspected RLD (left visual field advantage ≥ 20 ms) were invited to participate in the MRI session alongside controls with a similarly large right visual field advantage. We limited inclusion to left-handers, because they are significantly more likely to present with RLD compared with dextrals (14).

Since we selected our participants based on their presumed language dominance, we first compared how LLD and RLD subgroups were lateralized for each of the four other functions. We next determined each participant's pattern of hemispheric functional segregation and once again compared these patterns between language dominance subgroups. Finally, we explored whether language dominance and hemisphere functional segregation patterns were behaviorally relevant by relating them to measures of neurocognitive performance.

Results

Participants. A total of 315 participants completed the visual half-field task (mean age, 20 ± 2.08 y; 76.5% female), of whom 63 (20%) presented with a left visual field reaction time advantage ≥ 20 ms. Among these, 38 individuals participated in the MRI session. Based on the outcome of the fMRI language task, 22 of them were classified as RLD (LI > 0) and the remaining 16 were classified as LLD (LI < 0). In addition, one participant with

a left visual field reaction time advantage of 5.6 ms was accidentally invited to participate in the MRI session due to an oversight during the recruitment phase but nevertheless turned out to be RLD according to the word generation fMRI task and thus was included in the RLD sample. We also recruited 24 left-handers with a right visual field reaction time advantage, whom the fMRI language task classified 23 as LLD and 1 as RLD. Thus, the final sample comprised 24 participants with RLD and 39 with LLD; Fig. 1 shows a flowchart of the recruitment process.

The LLD and RLD subgroups did not differ significantly in terms of age, sex distribution, years of education, or strength of handedness (Table 1). Note that the LLD participants with a left and a right visual field advantage on the visual half-field task did not differ from each other in terms of demographics, neurocognitive performance, or strength of lateralization on the five fMRI tasks (*SI Appendix*). All participants successfully completed the entire MRI scan session, except for 5 LLD participants who were unable to complete the emotional prosody task due to technical issues with the auditory stimulus delivery system.

Relationship between Language Dominance and Other Functional Asymmetries.

For each of the fMRI tasks, we calculated participant-specific laterality indices (LIs) to quantify the difference in activation between left and right brain areas. The LIs ranged from -1 (complete left hemisphere lateralization) to $+1$ (complete right hemisphere lateralization) and were determined within regions of interest (ROIs) known to be crucial for the investigated functions based on patient lesion studies.

To investigate whether language dominance is associated with the direction of hemispheric dominance of the other brain functions, we compared the LIs of the LLD and RLD subgroups (Fig. 2 A–E). Since the LIs were not normally distributed, the nonparametric two-tailed Mann–Whitney U test was used, which indicated that the LLD and RLD subgroups differed significantly in the median LI for all functions: praxis (LLD: median, -0.43 ; IQR, 0.43 ; RLD: median, 0.28 ; IQR, 0.34 ; $W = 117$; $P < 0.0001$; $r = 0.63$; 95% CI, -0.88 to -0.48), visuospatial attention (LLD: median, -0.47 ; IQR, 0.34 ; RLD: median, -0.26 ; IQR, 0.46 ; $W = 860$; $P < 0.0001$; $r = 0.70$; 95% CI, 0.48 – 0.86), face recognition (LLD: median, 0.07 ; IQR, 0.41 ; RLD: median, -0.17 ; IQR, 0.31 ; $W = 693.5$; $P = 0.0014$; $r = 0.40$; 95% CI, 0.09 – 0.37), and emotional prosody (LLD: median, 0.43 ; IQR, 0.43 ; RLD: median, -0.45 ; IQR, 0.44 ; $W = 725$; $P < 0.0001$; $r = 0.66$; 95% CI, 0.59 – 1).

We then calculated the proportion of left and right hemisphere dominant participants for each of these brain functions within the LLD and RLD subgroups (Fig. 2F). A series of χ^2 tests revealed significant between-group differences in the distribution of the direction of hemispheric dominance, indicating that compared with the LLD subgroup, participants with RLD are approximately 22.9 times more likely to be right hemisphere dominant for praxis [$\chi^2(1, n = 63) = 22$; $P < 0.0001$], 20.4 times more likely to be left hemisphere dominant for visuospatial attention [$\chi^2(1, n = 63) = 22.2$; $P < 0.0001$], 3.9 times more likely to be left hemisphere dominant for face recognition [$\chi^2(1, n = 63) = 4.7$; $P = 0.03$], and 23.3 times more likely to be left hemisphere dominant for emotional prosody [$\chi^2(1, n = 58) = 22$; $P < 0.001$].

Hemispheric Functional Segregation. In the next step of the analysis, we investigated the patterns of hemispheric functional segregation that emerged when participants were classified depending on how they were lateralized for each of the five functions. The resulting patterns and the frequency with which they occurred are shown in Fig. 3. Several observations are of interest. First, since each function can be either left or right hemisphere dominant, the number of theoretically possible combinations is $2^5 = 32$. Out of these, we observed 19 different combinations ($\sim 60\%$ of all possible combinations). Second, the pattern that occurred most frequently within the LLD subgroup was the typical pattern of

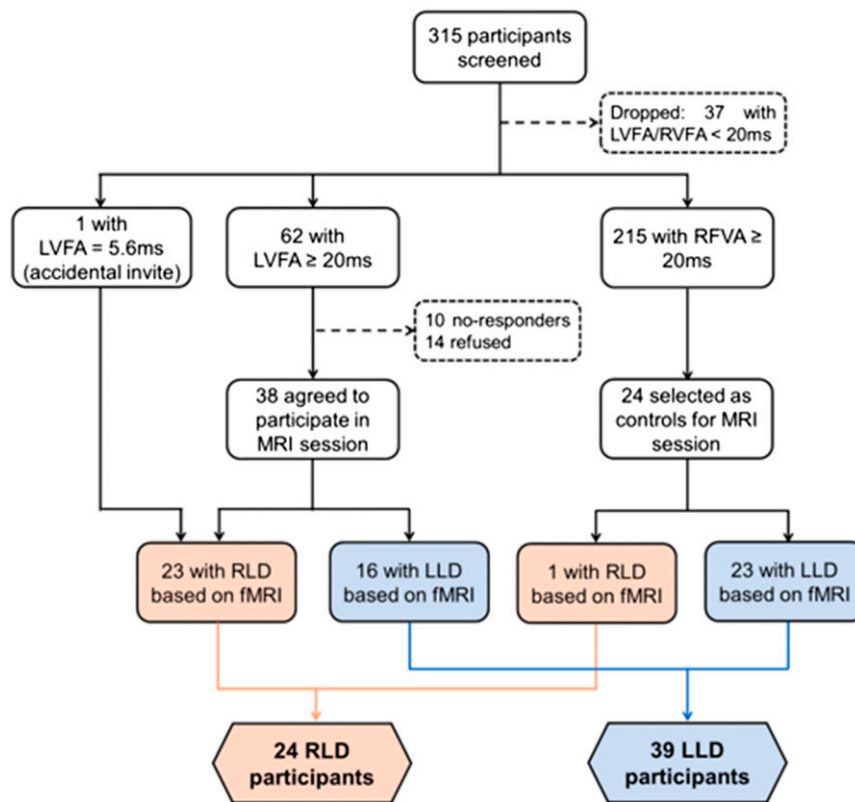


Fig. 1. Flowchart of study participant recruitment. LVFA, left visual field advantage; RVFA, right visual field advantage.

functional segregation ($n = 15$; 44% of LLD), where language and praxis lateralized to the left hemisphere and visuospatial attention, face recognition, and emotional prosody were dominant in the right hemisphere. In the participants with RLD, the most commonly observed pattern corresponded to a complete reversal of the typical functional segregation pattern ($n = 12$; 50% of RLD). Taken together, 27 participants (47% of the full sample) demonstrated a segregation pattern in which language and praxis lateralized to one hemisphere and the three other functions lateralized to the opposite hemisphere.

Third, the former implies that 31 participants (53% of the full sample) had at least one function that deviated from this segregation pattern, among whom 20 (34% of the full sample) showed only one deviating function and the remaining 11 (19% of the full sample) had two functions that deviated from the (reversed) typical functional segregation pattern. Finally, the χ^2 test indicated that the distribution of (reversed) typical functional segregation, one deviation pattern, and two deviation patterns did not differ significantly between the LLD and RLD subgroups [$\chi^2 (2, n = 58) = 0.66; P = 0.72$].

Hemispheric Language Dominance, Hemispheric Functional Segregation, and Neurocognitive Performance. To assess whether the direction of hemispheric language dominance is related to neurocognitive

performance, we compared the performance of the LLD and RLD subgroups on an intelligence test (Raven's Standard Progressive Matrices [RPM]), a general cognitive test battery (Repeatable Battery for the Assessment of Neuropsychological Status [RBANS]), and two specific high-level language tasks (verbal fluency and vocabulary knowledge). As shown in Fig. 4A, no significant between-group differences were found for any of these tests.

We next explored whether the patterns of functional segregation that we identified were associated with neurocognitive performance. To this end, the participant sample was divided into four subgroups: typical functional segregation ($n = 17$), reversed typical functional segregation ($n = 12$), and one deviation ($n = 23$) and two deviations ($n = 10$) from (reversed) typical functional segregation. Given the small sample sizes of the four subgroups, the nonparametric Kruskal–Wallis test was used. The Kruskal–Wallis test found no significant effect of functional segregation on RPM performance [$H (3, n = 58) = 3.34; P = 0.34; \eta^2 = 0.007$] (see Fig. 4B), but did reveal a significant effect on the RBANS performance [$H (3, n = 58) = 14.9; P = 0.0019; \eta^2 = 0.22$] (Fig. 4C). Post hoc comparisons using a Benjamini–Hochberg corrected two-tailed Dunn's test indicated that the RBANS performance was significantly lower in the two deviations subgroup (median, 93; IQR, 12) compared with the typical functional segregation subgroup (median, 110; IQR, 12.5; $W = 3.31; P = 0.003$; median difference [D], -16), the reversed typical functional segregation subgroup (median, 106; IQR, 7.25; $W = 2.34; P = 0.039; D = -12$), and the one deviation subgroup (median, 108; IQR, 20; $W = 3.63; P = 0.002; D = -15$). The other comparisons did not reach statistical significance (typical vs. reversed typical functional segregation: $W = 0.90, P = 0.44, D = 4$; typical functional segregation vs. one deviation: $W = -0.12, P = 0.903, D = 1$; reversed typical functional segregation vs. one deviation: $W = -1.08, P = 0.42, D = -3$). Taken together, these results

Table 1. Characteristics of the LLD and RLD subgroups

Characteristic	LLD	RLD	<i>P</i>
Age, y, median (IQR)	20 (4.06)	20 (4.00)	0.82
Sex, % female	90	88	1
Education, y, median (IQR)	14 (3.00)	14 (3.03)	0.87
EHI, median (IQR)	-90 (20)	-100 (10.25)	0.10

P, P value of the χ^2 test (sex) or Wilcoxon test (other characteristics); EHI, Edinburgh Handedness Inventory score.

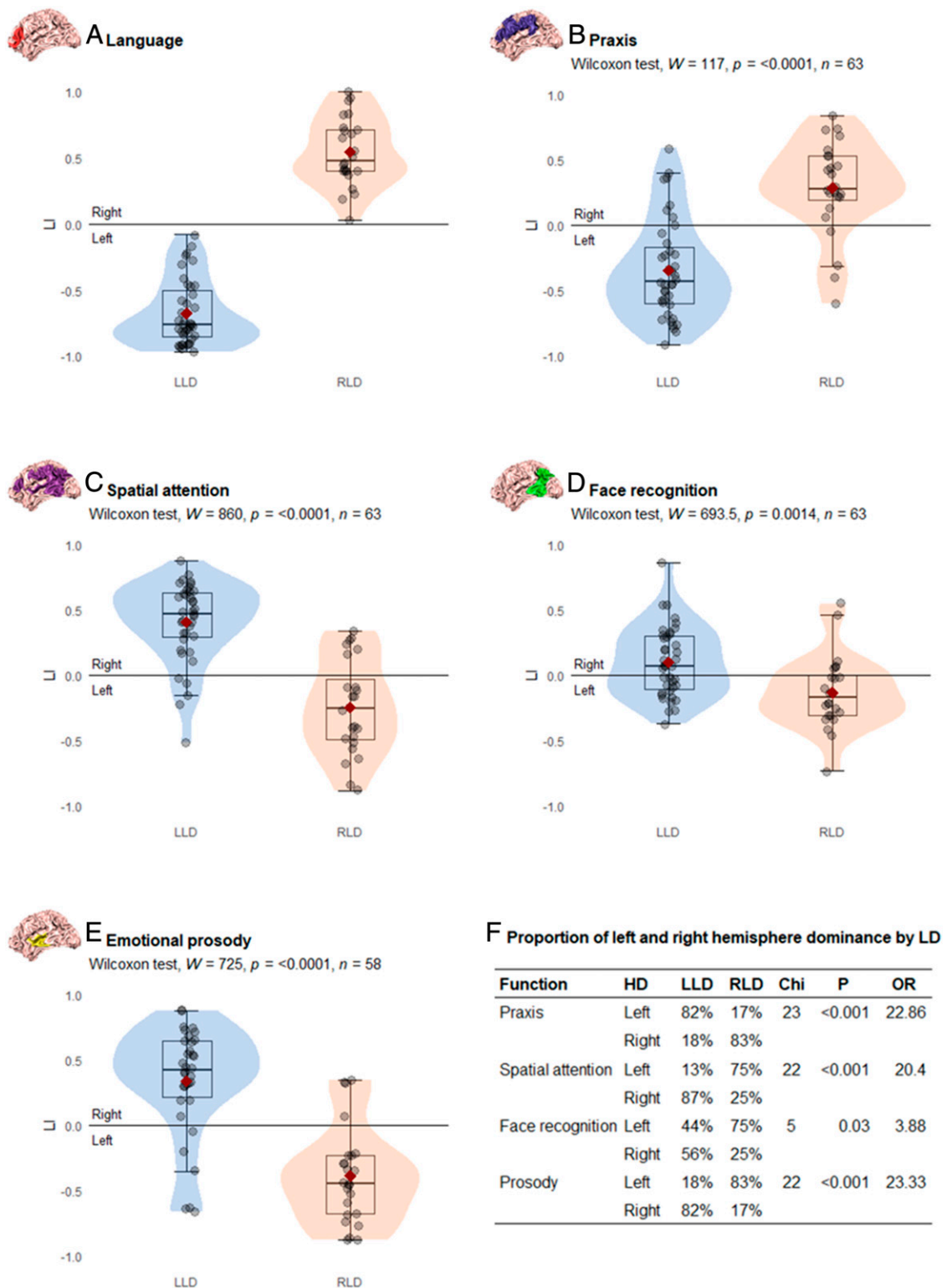


Fig. 2. Language dominance and hemispheric dominance of the other functions. (A–E) Distribution of the LIs of the word generation task (A), tool pantomime task (B), landmark task (C), face recognition task (D), and emotional prosody task (E) in the LLD (blue) and RLD (pink) subgroups. The violin plot’s diamonds and bold lines denote the mean and median values, respectively; whiskers represent the IQRs. Results of the Wilcoxon test comparing subgroup medians are provided above the violin plots. The ROIs within which the LIs were calculated are depicted next to each violin plot. (F) Table detailing, by function, the distribution of left and right hemisphere-dominant individuals conditioned on language dominance. HD, hemisphere dominance; chi, χ^2 statistic; OR, odds ratio indicating how likely RLD participants are to be typically lateralized compared with the LLD participants.



Fig. 3. Patterns of functional segregation. (A) Frequency of each hemispheric functional segregation pattern across the whole sample. Functional asymmetries are represented by a letter within a circle: L, language; P, praxis; S, spatial attention; F, face recognition; E, emotional prosody. Each box on the x-axis corresponds to a specific segregation pattern, in which functions above the line lateralize to one hemisphere and functions below it lateralize to the opposite hemisphere. (r)TFS, typical segregation pattern or its mirror reversal; 1-dev, one deviation from (r)TFS; 2-dev, two deviations from (r)TFS. (B) Frequencies of (r)TFS, 1-dev, and 2-dev patterns within the LLD and RLD subgroups.

indicate that the subgroup with two deviations performed significantly worse on the RBANS compared with all other functional segregation subgroups.

Discussion

Little is known about the relationships between lateralized functions, in part because there is a paucity of studies measuring multiple functional asymmetries in the same individuals (2, 22). The present study used fMRI to determine hemispheric dominance for five different functions in a group of left-handers with either LLD or RLD. We found that language dominance strongly predicted the direction of hemispheric asymmetries of the other functions, as RLD significantly increases the likelihood that they will show atypical lateralization just as well. These

results thus confirm and extend earlier findings in left-handers preselected on their language dominance (31–33). Similarly, the vast majority of our participants displayed a complete (typical or reversed typical functional segregation, 47%) or nearly complete (one deviation, 34%) prototypical pattern of hemispheric functional segregation, albeit left-right flipped in the RLD subgroup. While this suggests the existence of a population bias toward maintaining typical hemispheric functional segregation, the observation that one-half of the participants deviated from this pattern in one function or (less commonly) two functions implies that this bias is not completely obligatory but is subject to at least some variation.

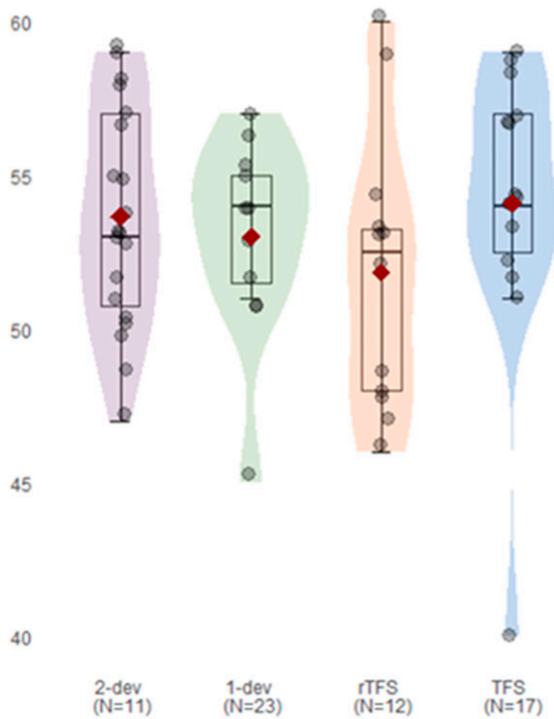
At first glance, the elevated rates of atypical hemisphere dominance in RLD might be taken as support for the causal

A Performance stratified by language dominance

Test	LLD	RLD	Statistic	p	Eff
RPM	54 (4)	53 (4)	490(a)	0.766	0.04
RBANS	106 (11)	105 (11)	0.99	0.325	0.26
Fluency	86 (15)	80 (13)	1.42	0.162	0.37
Semantics	NA (NA)	53 (12)	0.22(b)	0.829	0.06

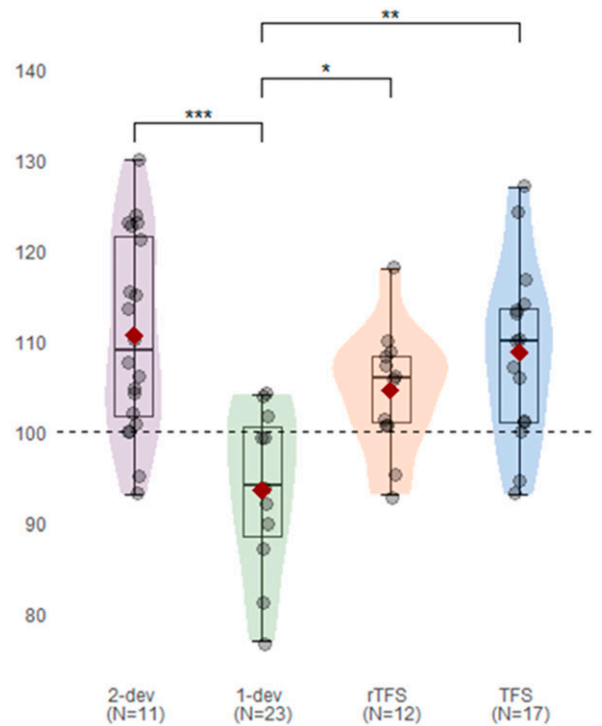
B RPM stratified by functional segregation

Kruskal-Wallis, $\chi^2(3) = 3.32, p = 0.34, n = 58$



C RBANS stratified by functional segregation

Kruskal-Wallis, $\chi^2(3) = 16.59, p = 0.00086, n = 58$



Post-hoc comparisons

Group 1	Group 2	D	W	p
rTFS	TFS	-4	0.90	0.440
2-dev	rTFS	-12	2.38	0.035
	TFS	-16	3.38	0.002
1-dev	2-dev	15	-3.85	0.001
	rTFS	3	-1.25	0.319
	TFS	-1	-0.31	0.758

Fig. 4. Neurocognitive behavior. (A) Comparison of the LLD and RLD groups' performance on the RPM (number of correct items), RBANS total score (standard score), verbal fluency task ("fluency"; number of words generated), and vocabulary test ("semantics"; number of correct items). Test statistics, *P* values (*p*), and effect sizes (Eff) are reported for two-tailed, two-sample *t* tests unless specified otherwise (a, two-tailed Wilcoxon test; b, two-tailed Welch test). (B and C) Comparison of functional segregation patterns on RPM (B) and RBANS (C) performance. The statistical significance of post hoc comparisons are indicated by asterisks: **P* < 0.05; ***P* < 0.01; ****P* < 0.001. The dashed line indicates the average score of the norming sample of the RBANS. C also shows a post hoc comparison table of all contrasts (two-tailed Dunn's test, Benjamini–Hochberg corrected for multiple testing). D, difference in median performance between group 1 and group 2; W, test statistic.

hypothesis of lateralization. However, strictly speaking, this hypothesis predicts that RLD always marks a complete hemispheric reversal, which instead was observed in only one-half of the cases. On the other hand, while the high variability in segregation patterns in the LLD subgroup is expected based on the statistical hypothesis, it has difficulty explaining why most participants with RLD demonstrated a (nearly) complete reversal of the typical hemisphere functional segregation pattern. If functions lateralized independently, as the statistical hypothesis proposes, it would be extremely unlikely that four—let alone five—functions would become dominant in the atypical hemisphere, given their strong population-level biases even in left-handers (14, 17, 19, 23, 36).

Since neither the statistical nor the causal hypothesis can fully account for the pattern of data found in the present study, we offer an alternative explanation. We propose the existence of a segregation bias that pressures the brain to develop according to a blueprint that outlines how functions should segregate (2). While in most people, this building plan is oriented to materialize according to the standard typical functional segregation pattern, it is mirror-reversed in a minority of people, biasing them toward reversed typical functional segregation. The direction setting of the segregation bias is likely determined early in ontogenesis, similar to left-right symmetry breaking of the visceral organs (37, 38). Following cerebral left-right symmetry breaking, functions will lateralize according to independent, probabilistic mechanisms, much like

those proposed by the statistical hypothesis. As a result, individuals with a typical segregation bias and those with a left-right flipped segregation bias will occasionally deviate from complete typical and reversed typical functional segregation, respectively, as was observed in the present study. This hypothesis allows our results to be reconciled with studies concluding that multiple independent factors contribute to functional asymmetries based on factor analyses in samples not enriched with RLD participants (17, 39, 40).

The same independent factors could be at play in the RLD subgroup, assuming that the symmetry breaking event also reverses their directionality. Moreover, if it is assumed that reversal of segregation bias also applies to handedness, then our hypothesis also would contribute to the explanation as to why left-handers as a group display more directional variability in their hemispheric asymmetries (41).

It is commonly assumed that the prototypical division of labor between the cerebral hemispheres presents an evolutionary efficient solution to organize the brain (12, 13). Two observations in the present study might be considered to support this idea. First, participants with typical and reversed typical functional segregation generally showed similar above-average performance on measures of intelligence and general cognition. Second, while the brain is seemingly able to handle one deviating function without any apparent neurocognitive repercussions, participants with two deviating functions performed significantly worse on a neuropsychological test battery (RBANS) compared with participants with (reversed) typical functional segregation or those with only one deviating function. This finding replicates a recent study in individuals with total reversal of their visceral organs (*situs inversus totalis*) and matched controls that revealed increasingly suboptimal performance on the RBANS in participants with increased atypical functional segregation over and above the effect of visceral condition (42). Further support for a link between hemisphere functional segregation and cognition was provided by Powell et al. (43), who reported a disadvantage for verbal comprehension and perceptual organization skills when language and spatial attention crowded in the same hemisphere. Taken together, these results suggest that the pattern of hemispheric functional segregation seems more informative about cognitive ability than the direction of hemisphere asymmetries per se. In a similar vein, we found no association between language dominance and any of our performance measures, including language proficiency tests, in agreement with earlier studies (44, 45; but see ref. 43 for a conflicting report).

Our findings raise a host of questions to be addressed by future research. First, are some patterns of atypical functional segregation more common than others? Based on our data, the tentative answer to this question would be “yes,” as crowding between face recognition and language/praxis accounted for one-half of all patterns in which only one function deviated from (reversed) typical functional segregation. A larger sample is needed to obtain reliable population estimates of each pattern’s prevalence, however. Second, are different hemispheric segregation patterns associated with specific advantages or disadvantages? It may be the case, for instance, that hemispheric crowding will come at a higher neurobehavioral cost when the crowding functions have high computational redundancy and/or otherwise would have occupied homotopic brain regions, since these functions will be competing for processing resources or neural space (2). Third, how does the profile of hemispheric functional segregation patterns look in right-handers? Presumably, they will display a higher proportion of typical functional segregation, given their overall lower phenotypic variability and stronger population-level lateralization biases compared with left-handers (41). Finally, the potential link between nontypical variants of hemispheric functional segregation and cognition has societal implications that warrant further research, for example, by investigating the extent to which atypical segregation might constitute a risk factor for developmental disorders (46).

Materials and Methods

Participant Recruitment. A behavioral visual half-field task was used to screen a large sample of left-handers for RLD (35). During this task, participants were instructed to name out loud written words presented either to the left or right half field as quickly as possible. As visual stimuli are projected to the contralateral visual cortex, faster and more accurate responses to words in the right visual field compared with words in the left visual field indicate LLD. Conversely, a relative advantage for naming words in the left visual field is indicative of RLD. All left-handers with a left visual field reaction time advantage >20 ms were invited to participate in the fMRI session. We also recruited left-handers with a similarly large right visual field reaction time advantage from the same sample to serve as controls with LLD.

Eligibility criteria for this study included self-reported left-handedness, age between 17 and 35 y, normal or corrected-to-normal vision, and no history of developmental disorders or brain surgery. To obtain a sufficiently large sample of left-handers for the screening session, we recruited both undergraduate students who participated for course credits as well as paid volunteers. The latter group was reached via a research website, social media, word of mouth, flyers put up in local public spaces/businesses, and advertising during local public science events. All participants were pursuing or had completed a college or university degree.

The study was approved by the Medical Ethics Committee of Ghent University Hospital. Written informed consent was obtained from each participant after the nature and possible consequences of the study were explained, in accordance with the Declaration of Helsinki.

fMRI Paradigms. We used fMRI to obtain participant-specific measures of hemispheric dominance for language (word generation task), praxis (tool pantomime task), spatial attention (line bisection judgment task), face recognition (dynamic faces one-back task), and emotional prosody (emotional intonation judgment task). A recent study showed that fMRI can reliably quantify hemisphere asymmetries (47).

Word Generation Task. Language lateralization was determined using a covert letter verbal fluency paradigm (32). This paradigm consisted of seven cycles, each consisting of a word generation block and a control block, separated by a rest block. During the word generation blocks, participants were asked to think about as many words as possible starting with a letter presented in the middle of the screen. Seven letters were selected based on a pretest with native Flemish-Dutch speakers (b, d, k, m, p, r, and s). The control task consisted of silently repeating the meaningless string “baba” which was projected on the screen. During the rest blocks, which were indicated by a small horizontal line in the middle of the screen, participants were instructed to relax and not think of anything in particular. All blocks lasted 15 s, and the task took 7 minutes to complete.

Tool Pantomiming Task. Lateralization for manual praxis was assessed using a tool pantomiming paradigm in which the participant mimics an instrumental grasp and movement with an imaginary tool object (31). All stimuli in this task consisted of two tool object pictures, one presented to the left side and the other to the right side of the screen. In the “tool” blocks, the two objects depicted familiar tools that are often used together, such as a pencil and a sharpener. Participants were asked to pantomime the use of these tools according to their position on the screen. For example, if a pencil was shown on the left and a sharpener on the right, the participant had to pretend to use the left hand to sharpen a pencil while holding the sharpener in the right hand. Since in most of these bimanual actions, one hand has a clearly active role and the other hand has a more passive role, the object positions are switched for one-half of the stimuli, thereby controlling for effector bias. In the control blocks, included to control for general object-related movement, participants pantomimed a bimanual rotating movement following simple object cues (eggs). Again, effector bias was accounted for. The participant was instructed to perform the pantomimes calmly to avoid motion artifacts. This paradigm included a total of four conditions, each characterized by a different combination of object type (tools vs. eggs) and the hand performing the active action (left vs. right). Each of the four conditions consisted of seven blocks ordered in a pseudorandomized manner to avoid consecutively presenting blocks with the same type of stimuli. All blocks lasted 21 s and were composed of six stimuli of 3,500 ms each; thus, completing the entire task took 9 min 48 s.

Line Bisection Judgment Task. Hemispheric dominance for spatial attention was established using a line bisection judgment (“landmark”) paradigm (48). During this paradigm, a task block, a control block, and a rest block were

presented consecutively for six cycles. Each 26-s block consisted of 12 trials of 1.6 s presented in random order with an intertrial interval of 200 ms. Stimuli in the task and control blocks consisted of a black horizontal 15-cm-long line and a short vertical line ("mark") presented on a white background. During the task block, the vertical mark was centered on the horizontal line. In one-half of the trials, the mark was positioned in the exact middle of the horizontal line, while in the remaining trials, the mark deviated to the left or the right by 2.5%, 5.0%, or 7.5% of the length of the horizontal line. The participants were instructed to press the left and right response buttons simultaneously only when the vertical line was bisected exactly.

In the control block, the same stimuli were used, except that in one-half of the trials, the vertical mark was positioned slightly above the horizontal line and in the other half, the vertical mark touched the horizontal line. Participants were instructed to press the left and right response buttons simultaneously if the vertical mark contacted the horizontal line. The rest block between the task and control blocks consisted of a fixation cross. The paradigm took 7 min 48 s to complete.

Dynamic Faces One-Back Task. Laterality for face recognition was determined using an n-back task (49). Participants viewed blocks of 2-s video clips of faces or inanimate objects and were instructed to press the left and right response buttons simultaneously each time a viewed video was identical to the one shown previously. Clips in the face blocks displayed dynamic changes in facial expression, either from neutral to happy or from neutral to sad. In the control blocks, the object video clips displayed movements that avoided large positional translations, to make the dynamic changes in objects comparable to those seen in the face clips. Each block lasted 12 s and consisted of six clips (five novel and one repeated). Seven face and control blocks were presented in a counterbalanced order. The total task took 5 min 54 s to complete.

Emotional Intonation Judgment Task. Hemispheric dominance for emotional prosody was assessed using an auditory decision task. During this task, emotional judgment and semantic judgment blocks were alternated, separated by 21-s rest blocks. In the emotional judgment blocks, speech stimuli produced with different emotional tones (happy, angry, sad, or scared) were presented. Participants were instructed to direct their attention to the intonation of the sentence and press the left and right response button simultaneously each time a sentence was pronounced in a happy way. During the semantic judgment blocks, sentences spoken with neutral prosody were presented. Participants had to focus their attention on the sentence content and press the left and right response button simultaneously when an action was described. Each task block consisted of 5 sentences and lasted 21 s. Seven emotional judgment blocks and seven semantic judgment blocks were presented.

The stimuli used in this task were created by first generating 80 Dutch sentences with neutral semantic content. All sentences were presented in the present tense and followed the same syntactic structure (subject, verb, noun phrase). Thirty participants next judged the emotional valence of the sentences to ensure their emotional neutrality. Four male and four female Flemish-Dutch native professional speakers subsequently produced the sentences with the intended prosody: happy, sad, angry, scared, or neutral. Finally, 20 participants rated the prosodic emotion of the speech stimuli. Only speech samples with an interrater agreement of $\geq 80\%$ were included in the fMRI task. The duration of stimulus ranged from 1,110 to 3,750 ms.

Behavioral Assessment. General cognitive performance was assessed using Dutch versions of the RBANS (50) and RPM (51). The RBANS consists of 10 cognitive subtests that contribute to five index scores: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. Performance on these index scores were combined into a summary measure (Total Scale), which was reported as a standard score with a mean of 100 and an SD of 15. The RPM is a multiple-choice test that assesses nonverbal abstract reasoning (52). It comprises 60 progressively difficult items consisting of 3×3 matrices of geometric designs, with one missing element. From a set of six to eight choices, the participant is instructed to select the design that completes the pattern in the matrix.

In addition, specific language skills were assessed using a Dutch vocabulary test and a verbal fluency test. The vocabulary test consisted of 75 items presented in a multiple-choice format with four answer alternatives (53). During the verbal fluency test, participants had to overtly generate as many Dutch words as possible within 1 min. First, letter verbal fluency was assessed, in which words starting with a given letter ("K", "A," and "N") had to be generated. Category verbal fluency was next assessed by instructing the participants to come up with examples from a certain semantic category ("animals" and "occupations").

fMRI Sessions. One-half of the participants completed the behavioral assessment before fMRI scanning, while the remaining half were scanned before neurocognitive performance was assessed. Each participant completed a pre-fMRI safety checklist and received detailed instructions about the tasks to be performed in the scanner before entering the scanner room. Example stimuli were presented for each fMRI task, and the importance of avoiding head movement during scanning was emphasized.

The fMRI data were collected on a 3.0-T Prisma scanner (Siemens) using a 64-channel head coil. A high-resolution T1 anatomic image of the whole brain was acquired using an MPRAGE sequence with 1-mm isotropic voxel size and 176 sagittal slices (repetition time [TR], 2,250 ms; echo time [TE], 4.18 ms; inversion time [TI], 900 ms; flip angle, 9°). Functional imaging consisted of T2*-weighted echo planar images acquired with the following scan parameters: 1-mm isotropic voxel size, 60 transversal slices, multiband factor 4; field of view, 210 mm; TR, 1,070 ms; TE, 31 ms; TI, 17 ms; flip angle, 52° . The language, praxis, spatial attention, face recognition, and emotional prosody tasks required the acquisition of 401, 560, 422, 321, and 465 volume scans, respectively.

fMRI Data Analysis. The fMRI data were processed using Brain Voyager version 20.3 (support.brainvoyager.com). Preprocessing consisted of slice timing correction, motion correction, temporal filtering, and coregistration to the T1-weighted MRI scan in MNI space using default parameter values. Next, a Gaussian smoothing filter was applied to the functional data (FWHM, 5 mm). An independent component analysis was then performed to identify noise components within the functional data for use in the generalized linear model. To obtain task-related predictors, the condition onsets were convolved with a canonical hemodynamic response function. A generalized linear model consisting of the task-related predictors and the nuisance predictors identified by the independent component analysis procedure was subsequently fit to the functional data. Finally, for each relevant task contrast, T maps were generated, which were used to calculate laterality indices.

Determination of Participant-Specific LIs. Participant-specific LIs were calculated for each fMRI task within Brodmann areas (BAs), which when damaged disturb the investigated function, as indicated by lesion studies: BA 44 and 45 for language (54); BA 6, 39, 40, and 44 for praxis (55, 56); BA 19, 22, 37, 39, 40, and 44 for spatial attention (57); BA 19 and 37 for face recognition (58); and BA 21 and 22 for emotional prosody (59).

To obtain participant-specific BAs, first the participant's segmented T1-weighted image was used to reconstruct the left and right cortical surfaces along the gray matter–white matter border. The resulting cortical meshes were visually inspected and manually corrected if necessary. Next, the individual's cortical surfaces were mapped to BrainVoyager template surfaces, on which BAs have been delineated as "patches of interest" (60). Participant-specific BAs were then obtained by applying the inverse transformation on template Brodmann patches. Finally, the BAs in surface space were transformed to 2D volume space, and the ROIs were constructed as defined above.

Lateralization indices were computed based on the magnitude of signal change (61, 62). First, a threshold was defined by taking the mean *T*-value of the 5% most active voxels over the left and right ROIs together and dividing this by 2. This threshold was then used to select "active" voxels within the left and right ROIs separately. The *T*-values of the active voxels for each hemisphere were then summed and divided by the number of active voxels within its ROI to adjust for the unequal size of the individually determined left and right ROIs. The LI was obtained using the following formula:

$$LI = \frac{Tsum_{Right} - Tsum_{Left}}{Tsum_{Right} + Tsum_{Left}}$$

where *Tsum* is the ROI size-normalized sum of the *T*-values of the active voxels within the ROI. LI calculation was performed using an in-house script (MATLAB release 2016b; MathWorks). A positive LI indicates right hemisphere dominance, whereas a negative LI signifies left hemisphere dominance. By using 0 as a cutoff, we avoided creating a third "bilateral" group, which would have implied specifying an arbitrary cutoff larger than 0.

Data Statement. The raw data and analysis scripts for this study are publicly accessible on the Open Science Framework via <https://osf.io/d872z>. All imaging data have been anonymized.

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