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Review

Phenotypes in hemispheric functional segregation? Perspectives and challenges

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Abstract

Directional hemispheric dominance has been established for numerous cognitive functions in the human brain. Strong population biases with some functions favoring the left and others the right hemisphere generated the popular idea of an advantageous prototypical division of labor between both halves of the brain, molded by evolution and genetically blueprinted. As most empirical studies on functional lateralization focused on a single function at a time, little is known about the relation between different asymmetric functions and the consequences of atypical functional segregation in healthy individuals. Recent investigations suggest the existence of at least three different phenotypes in human functional segregation relevant for future neuroscientific and genetic research. Using atypical language dominance as a starting point, I summarize the existing literature about its behavioral and neural consequences and explore the evidence for intermediate phenotypes in brain functional segregation that could bridge behavioral and genetic data.

Keywords: Functional segregation; Brain organization; Brain asymmetry; Atypical language lateralization; Functional lateralization; Language dominance

1. Introduction

Brain functional segregation refers to a division of labor between the two cerebral hemispheres. This pattern of functional asymmetry is explained in terms of conflict prevention of duplicate functional regions, enhancement of parallel processing, and increased neural capacity by eliminating redundant duplication [1–3]. Hemispheric specialization has been demonstrated in many animal species highlighting its role as a fundamental principle in the organization of behavior in vertebrates [4,5]. Besides asymmetric organization, the human brain also favors a prototypical hemispheric specialization at the population level with the left hemisphere being dominant for language, praxis, and calculation and the right hemisphere in support of spatial attention, face recognition, and prosody of speech. Each of these cognitive tasks engages a specific and widespread pattern of activation in both hemispheres. Nevertheless, the impact and

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Table 1
Percentage hemispheric dominance in left and right handers.*

	Right handers		Left handers		Population**	
	Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere
Language [6]	86	14	66	34	84	16
Praxis [7]	100	0	79	21	98	2
Spatial attention [8,9]	13	87	24	76	14	86
Face recognition [9–11]	13	87	22	78	14	86
Prosody [12]	21	79	33	67	22	78

* Several studies used cut-offs to define an additional category of bilateral representation, others didn't. If authors used a bilateral category, I split the percentage evenly between left and right representation to obtain a (rough) estimate of hemisphere dominance.

** Estimates based on the assumption of 90% right and 10% left hand preference in the human population.

persistence of functional loss following lateralized damage to core hubs of a function's 'dominant' hemisphere in the adult brain underpins the validity of functional brain asymmetry.

When considering population-wide functional asymmetries, it is important to point out that the widely proclaimed blueprint of human brain organization is almost entirely based on epidemiological research exploring asymmetries of a single cognitive function at a time. Percentages in Table 1 only present a dichotomized view of functional asymmetry and have been assessed by different methods in very different group sizes for the different functions listed. As a result, the proportions are merely indicative and should be interpreted with caution.

While the data in Table 1 offer hemispheric dominance estimates for each cognitive function and reveal differences between right and left handed individuals, they do not provide information on the relation between different asymmetric cognitive functions. One way to find out more about the mechanism and relevance of typical hemispheric functional segregation is to investigate individuals with atypical functional lateralization. As shown in Table 1, these individuals represent a substantial minority in left handed people and are also present in some right handers. As most lesion and imaging studies on atypical lateralization focused on a single cognitive domain, we don't know if atypical lateralization of a particular function is a statistic phenomenon that is sporadically scattered over the population with no effect on other functions, or whether it is clustered in the same individuals that show atypical lateralization of more than one (perhaps all) cognitive functions. Only a handful of studies explored the lateralization of two or more functions in the same individuals and their results will be detailed later. For now, I conclude that, despite popular belief, the relation *between* lateralized cognitive functions in the human population is largely unknown.

Before discussing the broader issue of hemispheric segregation of multiple functions, it is important to explore the concept of typical and in particular atypical functional lateralization of a single function. As most research on brain asymmetry has centered on language lateralization I will first explore this phenomenon before making the link to other functional asymmetries.

2. Atypical language dominance

2.1. What is meant by atypical language dominance?

While left hemisphere language dominance (LLD) is observed in the vast majority of humans and therefore taken to reflect typical language lateralization, atypical language lateralization is used by most researchers to describe individuals that show either right hemisphere language dominance (RLD) or in which no hemispheric dominance can be determined and bilateral representation of language function (BLR) is assumed.[1] While merging the relatively small samples of RLD and BLR individuals into a single group makes sense from a statistical perspective, such an heterogeneous 'atypical' group hinders correct interpretation of behavioral and neuroimaging data. Instead of categorizing (or dichotomizing) individuals based on hemispheric dominance, the better option is to present raw distribution data

[1] A major problem in the distinction between different types of language lateralization is that different cut off points are used by different researchers and that there is no common definition to separate BLR from LLD or RLD. Differences in categorization influence interpretation and burden comparison of results.

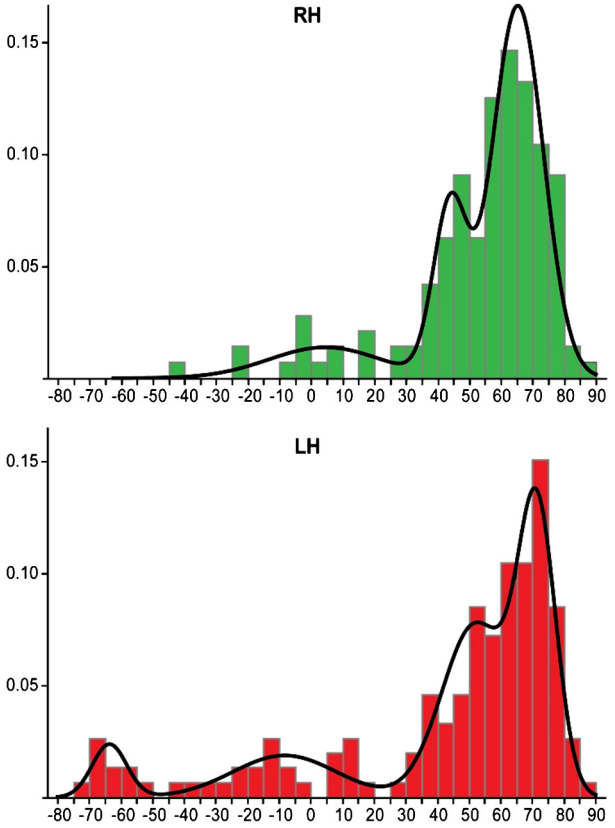

Fig. 1. Distribution of language lateralization in right handers (RH, top) and left handers (LH, bottom) as described in Mazoyer, B. et al., Gausian Mixture Modelling of Hemispheric Lateralization for Language in a Large Sample of Healthy Individuals Balanced for Handedness, Plos One, 2014;9. Solid lines represent fits of these distributions by Gaussian mixture modeling. Both handedness groups reveal a majority of LLD (hovering around a lateralization index of +65) and a smaller group with BLR (hovering around 0). Only left handers have an additional distribution of RLD-individuals (hovering around −65). Reprinted with permission from the authors.

based on lateralization indices,[2] and accept its associated measurement noise (only very few information is available on test-retest reliability of nearly all types of lateralization indices, but see [13]). Gaussian modeling suggests that RLD and BLR individuals represent two different phenotypes with increased frequency distributions along the middle and right dominant side of the laterality spectrum (Fig. 1) [14]. Qualitative differences also appear from this approach, with BLR observed equally in right and left handed individuals whereas RLD seems to occur almost exclusively in people with left hand preference. In addition to epidemiological research and assuming that BLR is not a consequence of measurement error, some evidence suggests that degree, not direction of lateralization, predicts performance and that absence of clear functional lateralization results in reduced task performance with BLR individuals performing worse than LLD and RLD participants [15,16]. Together, these arguments encourage careful use of 'atypical language dominance' as an overarching term for RLD *and* BLR individuals and to make a distinction between both types where possible.

[2] A lateralization index expresses left/right differences in a single measure. It usually takes the form $((R - L)/(R + L))100$, in which the laterality calculated by the numerator is weighted relative to the number of observations in the denominator. As there is no consensus on what the best measure of language asymmetry is, R and L values may be behavioral data (for example, the number of reported stimuli presented to the right or left ear in a dichotic listening task) or neuroimaging data (for example, the number of activated voxels in left and right Broca's regions in a word generation task during fMRI). Because some researchers prefer to calculate the numerator as L–R (unfortunately there is no consensus on this either), a lateralization index's minus sign may denote left hemisphere dominance in some papers and right hemisphere dominance in others.

2.2. Is atypical language dominance associated with left handedness?

Based on neuroimaging data, LLD is observed in close to 90% of the general population [14,17,18]. And although the majority of right *and* left handers show LLD, this is true in slightly over 90% of right handers, whereas lefthanders show up to 70–75% LLD.[3] While these percentages may hint at a relation between handedness and language lateralization, epidemiological research suggests that the group difference is almost entirely explained by the existence of an exclusively left handed group of individuals with RLD. Put differently, apart from the left handed RLD group, hand preference and language dominance appear unrelated [14]. Right handers with 'atypical' language dominance thus seem to consist of individuals with BLR only, whereas lefthanders with atypical language dominance consist of a proportionally equally sized BLR group as in right handers (about 10–15%) plus an even smaller sized group with RLD (6.5%), a condition that seems absent in right handers. Based on neuroimaging data in healthy participants, the answer to the question heading this paragraph thus appears to be yes, but only in individuals with RLD, not BLR.

Are there really no right handers with RLD? Reports on RLD in healthy right handed participants are extremely rare. The Groupe d'Imagerie Neurofonctionelle (GIN) in Bordeaux investigated 144 right handers using fMRI and found no one with RLD (defined as having a lateralization index $<-.50$) [14]). Knecht et al. investigated 188 right handed participants using fTCD and reported 14 (7.5%) to have RLD, but they applied a more liberal cut-off of about $-.20$ to determine RLD [18]. Applying the GIN-study cut-off to the Knecht et al. data would also yield no right handers with RLD as no one in the latter study had a lateralization index $<-.50$. Patient studies have documented several cases of crossed aphasia in dextrals but many reports appear unreliable because they lack essential data for correct diagnosis. In 2004 Peter Mariën and colleagues [19] critically reviewed potentially acceptable cases of crossed aphasia in dextrals and employed five essential criteria to classify patients as unreliable, possible, or reliable crossed aphasic right handers: (1) evidence of lesions confined to the right hemisphere, (2) evidence of aphasia, (3) evidence of right handedness, (4) absence of prior brain damage, and (5) absence of familial left handedness or ambidexterity. Of 152 right handed adults with crossed aphasia due to cerebrovascular lesions published world-wide since 1975, only 49 (32%) were considered reliable crossed aphasia dextrals. Compared to vast numbers of right handed people suffering right hemisphere cerebrovascular lesions each year, the publication rate of less than two reliable crossed aphasia cases each year suggests that dextrals with RLD exist but that the condition is quite rare.

To summarize, while clear RLD is observed in a subgroup of left handers in healthy individuals (ranging from 6–27% in the left handed population depending on the source [14,17,20]), its prevalence is far less frequent in right handers although it is occasionally reported in clinical cases of crossed aphasia.

2.3. Is there a genetic link between left handedness and atypical language dominance?

The genetics of human brain and behavioral lateralization remains poorly understood [21]. Most genetic models on functional asymmetry focused on hand preference as it is relatively easy to determine and allows an epidemiological approach. The earliest genetic models on handedness involve relatively simple mechanisms that incorporate a random component able to explain opposite handedness in monozygotic twins [22–24]. Annett's 'Right Shift' model proposes distributions of manual ability under the genetic control of two alleles, the RS+ and RS− gene, the RS+ being the dominant one. Genotypes RS+/+ and RS+/− result in a shift of the normal distribution to the right giving rise to right handedness in the majority of these individuals, with the right shift effect being stronger in the RS+/+ genotype than in the RS+/− genotype. The RS−/− genotype lacks this right shift and half of these individuals will become left handed. According to Annett, the population's handedness distribution is the result of three normal distributions, one centered at zero and the other two shifted to the right. McManus proposed a similar mechanism involving two alleles at a single locus, C (for chance) and D (for dextral). In its homozygous form DD results in *all* right handers and no left handers (not *most* right handers like RS+/+ of Annett's model would predict). As C is hypothesized to cause no effect on lateralization and the model takes fluctuating asymmetry as its starting point, exactly 50% of all CC individuals would be right handed and 50% would be left handed. The model does not define how heterozygotes DC individuals would manifest phenotypically but assumes that they would have between 0 and 50% chance of being left handed. McManus thus explains the population's distribution as the sum of two normal

[3] The more conservative estimates of LLD in Table 1 are derived from a meta-analysis including lesion, behavioral, and neuroimaging methods.

distributions, one completely to the right of zero the other symmetrically to the left of zero [25]. Although the Annett and McManus models make somewhat different predictions on handedness distribution, they show many similarities. Both models also forwarded an opinion on the association of handedness and language dominance, although the lack of epidemiological data on language lateralization and co-transmission of handedness and language dominance limited adequate testing of their hypotheses. Annett posited that all RS+/+ and RS+/− genotypes would be LLD and that 50% of the RS−/− genotype would be LLD and 50% would be RLD. Similarly, McManus predicted that the DD genotype results in LLD for all individuals whereas the CC genotype results in chance allocation of functions to right and left hemispheres. Note that McManus expanded predictions to any other cerebral asymmetry due to the same gene, with the DD genotype resulting in typical lateralization (language to the left, spatial attention to the right, etc.) and the CC genotype resulting in (statistically independent) chance allocation of functions to left and right hemispheres. When it comes to language, both models predict a prevalence of RLD around 7% in right handers and around 30–35% in left handers [24].

Finding a single-locus gene responsible for handedness as suggested by the Annett and McManus-models should be straightforward, especially with the advent of large scale genome-wide association studies, but this has not been the case. Despite sufficient statistical power, molecular genetics has not revealed a single-locus gene for handedness [26]. Handedness is now considered a polygenetic trait and it is estimated that multiple loci are involved in the determination of hand preference [27,28]. The additive heritability effect of handedness also appears to be modest. In a large international twin study genetics accounted for about a quarter of the variance with the remainder accounted for by unique environmental effects [29]. A recent genome-wide association analysis of categorical hand preference in over 330,000 individuals of the general population, however, found no evidence supporting any of the previously suggested genes to be involved in hand preference and suggested that some or all of these findings may have been false positives [30].

The downfall of single gene explanations for handedness (and putative related functions) as well as the discovery of different genes involved in handedness and language lateralization brought their relation into question [31]. While hand preference and language lateralization seem related to the extent that atypical language dominance is seen more frequently in people with atypical hand preference [17,32], the distribution of language laterality appears virtually identical in right and left handers, with the exception of a small group of RLD-sinistrals [14]. In sum, while all available data support higher prevalence of atypical language dominance in left handers, the cause of this observation remains uncertain and the additive role of genes seems limited. Classifying genes associated with handedness or language lateralization into functional groups depending on their biological effects, an approach called gene ontology, reveals that handedness genes contribute mostly to structural development and diseases affecting the whole body. Language lateralization genes on the other hand contribute to activity-dependent cognitive processes and are engaged in mental and neurological diseases. As these gene ontology sets barely overlap between phenotypes, the findings were taken to support the idea that handedness and language lateralization might be ontogenetically independent phenotypes [33,34].

What started in the 1970s with single gene models based on phenotyping of hand preference and that tried to explain handedness and language dominance by the same genetic mechanism was not corroborated by contemporary molecular genetics. Not only did the genetic mechanism of hand preference appear far more complex than initially hypothesized, current analyses also offer little support for the assumption that handedness and language lateralization share a common genetic background. Despite the work done so far, exploring the genetic basis of human brain and behavioral lateralization is still in its infancy. For a discussion on how molecular genetics and genomics could contribute to a better understanding of human brain lateralization see [21].

2.4. Is right language dominance associated with atypical lateralization of brain structure?

In spite of the lack of clear genetic models to explain functional asymmetry, there have been several attempts to relate brain structural or morphological asymmetries to functional lateralization. In 1968, Geschwind and Levitsky reported that the planum temporale (PT), an area in the temporal cortex involved in auditory processing, was larger on the left in 65% of 100 postmortem adult brains (and whose handedness was unknown) and proposed this anatomical asymmetry compatible with the functional asymmetry of language [35]. Subsequent research has not confirmed this prediction as left and right language dominant individuals show almost identical structural PT asymmetries, reviewed in [36]. A recent study measured PT asymmetry and language lateralization in 287 healthy adults including partici-

pants with right ($n = 10$) and bilateral ($n = 37$) language representation [36]. Language lateralization was assessed with a language production and sentence listening task during fMRI. Significant positive correlations were observed only between PT asymmetries and regional functional asymmetries measured in surrounding areas while participants listened to the sentences. No correlations between PT asymmetry and BOLD-response in core language areas, such as the inferior frontal gyrus and/or posterior middle temporal gyrus, were found for either language task. The authors concluded that PT asymmetry does not explain individual variability in language dominance and cannot be considered a marker of language dominance at the individual level. The finding that leftward PT and temporal lobe asymmetry is already apparent in the last trimester of human gestation [37,38], which is well before the development of language, lends further support to the conclusion that PT asymmetry may be a specific structural adaptation to language but does not predict its hemispheric dominance. Recent evidence of similar PT asymmetries in MRI-scans of 96 baboons (Papio anubis), an Old World monkey, even questions the relationship between PT asymmetries and the emergence of language [39]. Other gray matter structures like the pars opercularis of Broca's area and the insula revealed leftward asymmetry in both LLD and RLD participants [40,41]. The only significant LLD/RLD group difference was observed in the insula, with larger insula volume/surface asymmetry in LLD compared to RLD individuals [40,42]. Insula volume asymmetry also correlated with neural response asymmetry during word generation [40]. As these findings come from relatively small groups of predominantly left handed participants, the relation between insular asymmetry and language lateralization remains to be confirmed.

Other efforts on structure-function coupling in language come from white matter studies. Structural asymmetries of the arcuate fasciculus (AF) were reported to correlate significantly with fMRI lateralization during language tasks in right handers [43–45]. Only one of the studies included left handers ($n = 13$) five of which had RLD [45]. As these RLD sinistrals also showed leftward arcuate asymmetry, the authors suggested that the reported white matter asymmetry is explained by structural asymmetry of the arcuate, but appears unrelated to language lateralization. In addition, it remains unclear whether AF asymmetries are already present in newborns and how AF development relates to language acquisition [46].

Gray and white matter structural asymmetries in core language regions are clearly present in the human (and non-human primate) brain, but there is little evidence that these macroscopic asymmetries predict individual language dominance as LLD and RLD participants reveal similar (leftward) structural differences. Given the means it takes to assess language dominance and the low prevalence of RLD individuals in the general population, even large scale studies are confronted with relatively small atypical samples. The available data suggest that if structure-function couplings do exist, they are likely to be (very) small, that it will take very large samples to demonstrate their existence, and that these markers will probably not be predictive of language dominance at the level of the individual.

2.5. Is right language dominance associated with atypical functional activation patterns?

Is the language network of people with right language dominance a mirror image of the activation pattern in LLD participants or are there differences? Knecht et al. used fMRI to investigate patterns of neural language activation in 7 individuals with LLD and 7 with RLD, none of whom had evidence of brain lesions. A phonetic word generation task demonstrated a mirror reverse pattern of BOLD-response in right- compared to left-hemisphere dominant subjects. Variability of the activation pattern was calculated for both groups by comparing each participant with all participants of their group. No increased variability in the activation pattern between participants with RLD compared to LLD was found, although statistical power to detect such differences in this early study appears limited [47]. Similar findings have been obtained for this task by others [48], and for other cognitive functions including spatial attention [49,50] and praxis [51]. Together, these results indicate that in healthy participants atypical lateralization can be understood as a mirror reversal of the standard activation pattern, not a qualitatively different pattern of organization. Recent findings in a larger group of 63 healthy participants confirmed right hemispheric engagement of classical language centers during fMRI word fluency performance in a subgroup of 11 atypical language dominant volunteers [52]. The atypical language dominant group showed some additional right hemisphere activation in the angular and middle temporal gyrus that was not observed in the left hemisphere homologues of LLD participants. This observation suggested to the authors that atypical language dominance has unique features and is not a simple mirror image of the typical left hemisphere pattern. Most (10 out of 11) participants of their atypical group, however, showed predominantly symmetrical language organization, again highlighting the need to distinguish between RLD and BLR subgroups as proposed earlier.

To summarize, despite being underpowered, the available data suggest that activation patterns elicited during word generation by RLD participants show a mirror reversed activation pattern in classical language regions and do not present with an alternative language network although BLR-participants might recruit some additional brain regions when performing language tasks.

2.6. What is the behavioral relevance of atypical language dominance?

One of the most puzzling findings on atypical language dominance is the discrepancy between reports of its behavioral relevance in clinical and healthy populations. Altered structural and functional hemispheric asymmetries in relation to language have been reported for a wide range of neurodevelopmental and psychiatric disorders (for a detailed overview see Chapter 12 in [53]). In most studies the term atypical dominance refers to reduced LLD in comparison to typically developing individuals, but in Box 1 I focus on findings of absent or reversed dominance. This body of research carried the idea that atypical functional dominance is associated with pathology and could give rise to cognitive, emotional, and social impairment.

Epidemiological studies on the other hand, revealed the presence of atypical language dominance in the general population where it was demonstrated by reliable methods in healthy individuals. These individuals were reported to have normal language acquisition and linguistic and artistic abilities, although empirical data to support this claim are very limited. Only one study tested the behavioral relevance of atypical language lateralization in 264 healthy participants, of which 31 showed BLR and 31 showed RLD as determined by functional transcranial ultrasonography [54]. The authors used subjective reports (f. e. how many foreign languages do you speak fluently) and obtained performance data (speed of linguistic processing) in a limited subgroup of 21 participants selected to represent the range of left to right language dominance [54]. No significant differences were obtained between participants with typical or atypical language dominance. The authors concluded that although the possibility of subtle linguistic effects cannot be excluded, no major anomalies of atypical language lateralization could be detected. Data on behavioral effects of atypical lateralization of brain functions other than language are completely absent.

Could there be a healthy and a pathological path of atypical lateralization? And if so, what are the differences? This question was addressed by Dorothy Bishop when she argued that atypical lateralization in neurodevelopmental disorders may not be the cause but the consequence of impaired functional development [55]. Her argument was based on differences in heritability and genetics between dyslexia and hemispheric lateralization and on observed cognitive normality in healthy atypical language dominant volunteers. The difference between atypical language dominance in cognitively unimpaired versus impaired individuals might thus be determined by the circumstances: a neurodevelopmental variant from the standard blueprint in the healthy, the result of anomalous language development in neurodevelopmental disorders. Although more research is needed to confirm that atypical lateralization should be regarded a consequence rather than a cause of dyslexia, the general conclusion seems to be that neurodevelopmental pathologies are probably not the most ideal groups to investigate the mechanisms and behavioral consequences of atypical functional lateralization in the general population.

Box 1. Atypical functional lateralization and psychopathology

It has been reported that children with developmental language impairment show increased RLD and BLR in core language areas during language tasks [56,57], but see [58]. Several studies have documented a higher prevalence of RLD in Autism Spectrum Disorders (ASD) compared to typically developing individuals [59–63]. Interestingly, typical leftward arcuate fasciculus volume asymmetry was reported to be reversed to rightward asymmetry in completely nonverbal ASD children [64]. Atypical rightward activation asymmetries during speech production have also been reported in stutterers [65]. Reduced left hemisphere dominance or rightward asymmetry for perception and production of language was found in schizophrenia patients [66]. In addition, schizophrenics also show reversed asymmetry for semantic encoding [67] and reduced or even inverted asymmetries for right hemisphere language functions like prosody of speech [68].

Increased prevalence of atypical language dominance, in terms of reduced and reversed asymmetry, appears to be rule rather than exception in neurodevelopmental and psychiatric conditions, but does the atypical asymmetry extends to other cognitive functions as well? Evidence for atypical lateralization of spatial attention and reduced right hemisphere lateralization for face recognition has been reported in dyslectics [69,70]. Atypical lateralization

of motor circuit functional connectivity has been described in ASD as well as a rightward shift of 10 out of 17 functional networks identified in resting state fMRI [71,72]. In schizophrenia, atypical asymmetry of face recognition and visuospatial attention has been reported [73,74]. Atypical lateralization seems not restricted to language functions in diverse pathological conditions, but data are limited, and no studies have investigated the lateralization of multiple functions at the level of the individual patient.

2.7. Is atypical language dominance associated with atypical lateralization of other brain functions?

This question addresses the important issue of a possible relationship between the lateralization of different functions. While many scholars agree with the idea of an innate bias driving laterality to explain brain functional asymmetry at the population level, differences in opinion emerge as to its mechanism. According to one view, asymmetries of functions reflect innate biases of independent sources, implying that functions lateralize independently of each other [75]. This 'multiple independent sources'-hypothesis predicts that atypical laterality of one function will have no consequences for the lateralization of other functions as they will be lateralized according their own particular bias.[4] Some studies reported absence of a relation between laterality for language and spatial cognition and interpreted their findings as evidence for the multiple independent sources-hypothesis [75–77]. Bryden and colleagues investigated the concurrent incidence of aphasia and spatial disorder in 270 patients with unilateral brain damage and concluded that both functions are statistically independent. Diagnoses were based on a full neuropsychological examination, but actual performance data were not provided [75]. Whitehouse et al. measured hemispheric specialization of language production and spatial memory in 75 participants (45 right handed) using functional transcranial ultrasound. The association between laterality for language and spatial memory based on cross-tabulation of their hemispheric dominance appeared not significant [77]. Also using functional ultrasound, Rosch et al. found no correlation between visuospatial and language lateralization in 20 healthy right handers [76]. Together, these findings suggest that complementarity exists only as a statistical probability determined by the innate source that directs its laterality and this is why the multiple independent sources-hypothesis is more widely known as the statistical hypothesis [78].

An alternative hypothesis was forwarded by Kosslyn who suggested the idea of two unilateral control systems, each innately lateralized to a different hemisphere, that serve as the initial seeds for a subsequent cascade of differentiation of subsystems that give rise to functional segregation between the hemispheres [79]. According to the 'dual seed'-hypothesis, individual differences emerge depending on the strength of the innate bias and the level of transhemispheric degradation of information of competing but increasingly specialized hemispheres. In addition, initial plasticity will prevent complementary functions to crowd in the same hemisphere and compete for neural space. Laterality of one core seed will thus increase the probability of crossed asymmetry of the other seed implying a causal pattern of complementarity. Alternative mechanisms have been proposed [80–82], but all posit an interaction between functions and predict a significant correlation in degree of lateralization of complementary functions. Badzakova-Trajkov and colleagues used fMRI in 155 participants (107 right handed) to determine lateralization of speech production, face processing and spatial processing in frontal, temporal and parietal lobes respectively. Low to moderate but nevertheless significant correlations were found between most functional asymmetries. Their correlation matrix suggested at least in part complementarity of some (i.e. speech production and spatial attention, speech production and face processing), yet independence of other functions (i.e. spatial attention and handedness, spatial attention and face processing) [9].

Despite the abundance of research on the lateralization of cognitive functions, only few studies addressed their relationship by assessing the lateralization of different functions in the same individuals. In a recent review of such studies, Bazdakova-Trajkov and colleagues compared the evidence for a causal or statistical pattern of hemispheric complementarity [78]. They conclude that most of the data seem to support the statistical hypothesis because (1) many studies do not find significant correlations between the lateralization of different functions, (2) independent factors account for significant variation across subjects, and (3) it allows for crowding of functions that seems to occur in a substantial part of the population and which is more difficult to explain by the causal hypothesis [78].

[4] Atypical lateralization of a function in an otherwise typically organized brain is called crowding. The phenomenon implicates that the hemisphere accepting this 'new' function will be more crowded with functional representations as it will store both its usual and the novel functions.

3. Different phenotypes of hemispheric functional segregation?

While the causal versus statistical complementary discussion remains to be settled by exploring the relation between magnitudes of functional lateralization, let us focus on patterns of functional segregation observed in studies that investigated at least two asymmetric functions in the same individuals. Two different approaches have been used to investigate the phenomenological representation of hemispheric functional segregation. In the first, asymmetry of at least two functions is assessed in a *random sample* of participants, although groups are sometimes enriched with left handers to increase the odds of atypical lateralization and explore the effect of hand preference on functional specialization. By random I mean that participants are not preselected on atypical brain functional lateralization. In the second type, participants are carefully *selected for atypical* lateralization of one function (usually language) to explore the lateralization of another function. I will describe the results of both approaches in the next two paragraphs.

3.1. Hemispheric functional segregation in unselected (random) samples

Bryden et al. investigated 270 patients (of which 140 left handers) with unilateral brain lesions and noted the presence of aphasia and spatial dysfunction [75]. They estimated that in right handers 73% of men and 55% of women showed complementary specialization (including 1% men and 9% women with reversed complementarity) while the remaining patients showed crowding of both functions in the same hemisphere. In left handers estimates were more difficult to make because of the incidence of bilateral representation. McNeely and Parlow recruited 73 healthy volunteers (including 7 left handers) and had them perform a linguistic and prosodic dichotic listening task [12]. Seventy-eight percent showed the expected right and left ear advantages for linguistic and prosodic stimuli respectively. Twenty-two percent showed reversed complementarity, and no one showed the same ear advantage for both types of stimuli. Flöel et al. investigated 75 healthy participants (of which 38 left handed) on lateralization of language and spatial attention using functional transcranial ultrasound [8]. Right handed volunteers showed typical functional complementarity in 95% of cases, a reversed pattern in 1 case, and non-complementary organization (both functions in the left hemisphere) in 1 case. Left handed participants displayed typical organization in 60% of cases, a reversed pattern in 3 cases (8%), and non-complementary organization in 12 cases (32%; both functions in the left hemisphere in 4 cases, and to the right in 8 cases). Crossed/atypical lateralization patterns were significantly more frequent in left handers. Whitehouse and Bishop investigated lateralization for language and spatial memory using functional transcranial ultrasound in 75 healthy participants (of which 27 left handers and 3 ambidextrous) [77]. About 25% showed crowding of both functions in the same hemisphere and no one showed reversal of the typical pattern. Badzakova-Trajkov et al. scanned 155 healthy participants using fMRI to measure asymmetrical activation for word generation, spatial attention, and face processing [9]. While the majority showed typical functional segregation, all other possible patterns of cerebral lateralization were observed. Only three participants showed reversal of all three functions, two of which were left handed. Rosch et al. used functional transcranial ultrasound to determine lateralization of word generation and spatial attention in 20 right handed participants [76]. Thirteen showed typical functional segregation, 4 showed crowding (2 to the left and 2 to the right hemisphere), and 3 had reversed complementarity. Groen et al. investigated 60 mostly right handed children aged 6–16 using functional transcranial ultrasound to determine lateralization of language and spatial memory [83]. Most (58%) had typical functional organization but 19 (32%) showed functional crowding (12 to the left hemisphere and 7 to the right), and 3 (5%) showed functional reversal. The authors also tested whether having language and visuospatial functions in the same hemisphere was associated with poor cognitive performance but found no evidence for this although children with left-lateralized language production outperformed other children on vocabulary and non-word reading regardless of the laterality of visuospatial memory. Zago et al. used fMRI to calculate lateralization of language and spatial attention in 293 healthy participants including 151 left handers. Most participants showed typical segregation (ten of which the reversed pattern), but a substantial number showed crowding of both functions to either the left or right hemisphere. A negative correlation between LIs of both functions was only observed in the subgroup of strong left handers [84].

A critical review of many of these studies could certainly raise issues of inadequate statistical power, missing details on proportion of groups showing atypical lateralization, selection of tasks whose lateralization bias is insufficiently validated, and as a whole the many different methods used to ascertain functional lateralization. Nevertheless, studies investigating at least two asymmetric functions in the same individual in random samples, whether it be brain damaged patients or healthy participants, confirm that the majority of people present with the typical functional segregation

pattern suggested by single function research. In addition, multiple-function studies reveal that atypical patterns tend to be of either a 'crowded-type' or a 'reversed-type'. In the crowded-type, functions that would normally be lateralized to opposite hemispheres now share the same hemisphere, whereas in the reversed-type functional complementarity is maintained albeit in a mirrored fashion. The overview also shows that atypical segregation is not extremely rare and is seen in many if not all tested functions, and that its behavioral consequences remain to be detailed.

3.2. Functional segregation in preselected atypical samples

An alternative way to investigate the relation between different functional asymmetries is to select individuals with documented atypical language lateralization, test them for lateralization of another function, and compare the results with those of a matched group of LLD. Two studies performed at Ghent University, Belgium recruited left handed individuals with atypical language dominance. As right hemisphere language dominance seems almost exclusively reserved to left handed individuals [14], the researchers screened left handed participants with a visual half-field task to identify individuals with probable atypical language dominance. In the majority of this subset of left handers RLD was subsequently confirmed by fMRI, and only these participants were included for further investigation. The first study revealed that *all* left handers with atypical language dominance also had atypical lateralization for spatial attention [48], whereas the second study reported atypical lateralization for praxis in *all* individuals with atypical language dominance [51]. As these two studies were conducted at the same department and shared eight atypical language dominant left handers who agreed to take part in both studies, *all* eight left handed individuals showed atypical lateralization of the three functions investigated, while no one showed atypical language dominance only. In a more recent study applying the atypical sample approach, the group at Ghent University investigated lateralization of the visual word form area and face recognition area in the fusiform gyrus using fMRI in a new sample of 27 participants of which 12 showed LLD, 12 showed RLD, and 3 were classified as having BLR. Most LLD participants were typically lateralized for faces and written words, while both functions tended to be reversed in participants with RLD [11]. Together, these data suggest that in left handers with RLD, atypical lateralization is not limited to language and reversal of other lateralized cognitive functions seems to be the rule rather than the exception. Put differently, in left handers atypical language dominance is much more likely to flag complete reversal of typical functional segregation than occasional atypical lateralization of just one function. These observations have led selected (atypical)-sample studies to interpret their findings in favor of the causal hypothesis, because while the causal hypothesis might have difficulties to explain crowding of functions in healthy individuals, the statistical hypothesis has problems in explaining a complete reversal of all functions in one individual. Even if this individual is a left hander and presumably lacking a genetic or innate influence as suggested by genetic models, chances are unlikely that all cognitive functions would show left-right reversion if functions lateralize completely independent of one another.

Additional evidence for a potential distinction between different types of hemispheric functional segregation comes from observations on brain asymmetries in people with typical versus reversed visceral organization (situs inversus totalis, SIT) [85,86]. The study aimed to explore whether visceral reversal in humans was associated with brain structural and functional reversals as seen in other species [87–89]. fMRI localizer paradigms were used to investigate lateralization of two typical left hemisphere functions (language and praxis) and two typical right hemisphere functions (spatial attention and face perception) in each participant. While over 60% of participants showed typical hemispheric lateralization of all four cognitive functions, participants with SIT showed significantly more atypical lateralization of one or two functions while the remaining functions were typically lateralized. In addition, and unrelated to SIT, two left-handed participants revealed atypical lateralization of all four tested cognitive functions, a condition that suggests a complete mirroring of the typical human pattern of brain functional organization (mens inversus totalis), hand preference included.

In sum, studies exploring hemispheric lateralization of multiple functions seem to suggest that while most individuals show typical functional segregation (TFS), variants on this standard blueprint are relatively common in the human population. These variants can take two different forms: Either they are a complete mirror reversal of typical hemispheric complementarity (what biologists may interpret as a manifestation of anti-symmetry), or they show atypical lateralization of some but not all functions which results in crowding of functions that would normally not share the same hemisphere. The important distinction between both variants is that in the former case standard functional segregation is maintained albeit in a mirrored fashion. I propose the term reversed typical functional segregation (rTFS) for this condition to stress preservation of functional complementarity. I also suggest restricting the term atyp-

ical functional segregation (AFS) for conditions in which normal functional segregation is lost and crowding ensues.[5] Atypical functional segregation appears to have a higher prevalence than reversed typical functional segregation and is observed in left *and* right handed people whereas reversed typical functional segregation seems paired with left hand preference.

3.3. Is atypical functional segregation associated with atypical functional activation patterns?

When more than one function is assessed, reversed typical functional segregation-type participants reveal the same homotopic functional activation patterns for all investigated functions than do typical functional segregation-type participants with the exception that they are mirror reversed [48,49,51]. But what with atypical functional segregation-type participants? How is the brain organized when typically segregated functions lateralize to the same hemisphere? Floël et al. selected atypical individuals from a large number of healthy subjects that were screened for hemispheric dominance of visuospatial attention and language using functional transcranial ultrasound [49]. Two participants were right-hemisphere dominant for both language and spatial attention and it was hypothesized that the intra-hemispheric distribution of activation would not differ from that of a control group of seven participants with a typical segregation pattern. The hypothesis was confirmed using fMRI as participants with both language and spatial attention lateralized to one hemisphere showed no differences in intra-hemispheric activation pattern during a visual-spatial attention task compared to subjects with a typical pattern of hemispheric dominance. In addition, both participants performed within normal limits on verbal and non-verbal behavioral tests.

A possible explanation of why crowding of spatial attention and language does not necessarily gives rise to atypical functional activation patterns is provided by an fMRI study that investigated lateralization of word generation, spatial attention, and face processing in 155 participants (of which 48 left handers) [9]. Overlaying the whole brain group activation patterns of the three tasks, it was shown that their activated areas were largely non-overlapping. Unfortunately, this was not further investigated in the individuals with atypical lateralization, but one could argue from this observation that atypical lateralization of one function might not necessarily be behaviorally disadvantageous if the neural space occupied by this astray function is not allocated to functions that typically reside in this hemisphere. Interestingly, in a later study the same group of researchers reported neurophysiological differences in callosal properties between participants with typical versus atypical functional segregation of language and spatial attention. Enhanced anisotropic diffusion in callosal fibers was especially evident in participants with crowding of both functions to the right hemisphere suggesting more heavily interconnecting hemispheres [90].

As mentioned in the previous paragraph, more convincing evidence for brain functional repercussion of crowding should come from studies that investigate crowding of typically segregated functions that occupy homotopic brain regions like face and word-form processing (fusiform gyri), linguistic and emotional speech comprehension (posterior temporo-parietal areas), or verbal and spatial working memory (inferior frontal and posterior parietal areas). Unfortunately, no such studies on crowding are available in dextrals but two studies on possible differences in the neural responses of such function pairs in RLD sinistrals may be informative. Axmacher et al. investigated the effect of language dominance on the neural representation of verbal and spatial working memory in 32 participants. The authors reported that RLD participants ($n = 8$) showed increased inter-individual variability of working memory related activations. In particular, RLD participants revealed increased right hemisphere activity in heterotopic verbal working memory regions compared to LLD individuals [91]. Gerrits et al. assessed lateralization of the BOLD-response during tasks of visual word form or face recognition in the fusiform gyrus in 12 LLD and 12 RLD sinistrals. While recognizing written words almost exactly mirrored asymmetries of RLD compared to LLD participants, more than 40% of RLD individuals revealed bilateral activation for face recognition (17% in LLD) instead of converting to left hemisphere dominance. The authors explained their finding as the result of a competition between a segregation bias (trying to segregate face recognition from word form recognition) and an evolutionary bias (reluctance to divert from the typical blueprint and keep face recognition in the right hemisphere), and which gave rise to an incomplete reversal in some of the RLD participants. They also offered an alternative explanation based on putative hemispheric processing differences, with the left fusiform gyrus being more geared toward feature processing and the right tuned

[5] Because of its low prevalence rTFS can also be regarded as an atypical variant of standard functional segregation, but functionally it makes sense to distinguish between rTFS and AFS and reserve the term AFS only for cases were functional complementarity is renounced.

to holistic processing, and which would suggest increased reliance on feature processing during face processing in some of the RLD-participants.

There appears to be a substantial lack of information of the effect of crowding on functional activation patterning in healthy participants. In function pairs that do not engage homotopic regions even when segregated in different hemispheres, like speech production and spatial attention, the few available data show no obvious distortion of standard neural activation patterns when these functions crowd in the same hemisphere. Data on crowding effects of typically segregated homotopic functions in healthy people is lacking, but findings on such function pairs in participants more likely to have reversed typical functional segregation (RLD-sinistrals) at least suggests higher reluctance toward complete reversal and more bilateral hemispheric engagement. Again, sample sizes are very limited and RLD-sinistrals may constitute a very specific condition in which case results may not be generalizable to the entire human population.

3.4. Is there a behavioral consequence of atypical functional segregation?

Despite anecdotal reports of normal cognitive performance of individuals with atypical lateralization [54,83], other evidence casts a different light on the behavioral relevance of atypical functional segregation. From an initially large sample of 231 healthy children aged 9–12 years, Hernandez et al. recruited 20 children with left hemisphere dominance for language and motor control (i.e. LLD right handers), 20 with left language dominance but right motor dominance (LLD left handers), 20 with right language dominance but left motor dominance (RLD right handers) and 20 with right hemisphere dominance for language and motor control (RLD left handers) [92]. Children with non-convergent laterality showed inferior reading speed, reading accuracy, and reading comprehension compared to those concordant for hemispheric language and motor control. Laterality of either factor alone, did not predict reading performance, only the joint consideration of both factors showed significant effect. Interestingly, no differences emerged between directional types of convergent and non-convergent groups suggesting that only convergence but not direction of convergence is relevant for reading performance.

In the recent study on individuals with reversed visceral organization, situs inversus totalis-participants with atypical functional segregation performed significantly worse on a neuropsychological test battery compared to SIT-participants with typical functional segregation who, in turn, performed significantly worse than control participants with typical visceral and cerebral organization. These findings suggest that both having SIT and having atypical functional segregation contributes to suboptimal cognitive performance. Interestingly, atypical lateralization of spatial attention and praxis (but not language) significantly predicted (reduced) cognitive performance. In addition, the degree of atypical lateralization was correlated with all cognitive subscales (including memory), suggesting a general rather than a specific effect of atypical functional segregation on cognition [86].

Few and conflicting data underline the need for a more thorough investigation of the behavioral relevance of atypical functional segregation in the general population. Especially since atypical functional segregation does not appear to be extremely rare, it may be feasible to inspect the effect of atypical functional segregation-subtypes on the cognitive profile.

4. Challenges of research on hemispheric functional segregation phenotypes

4.1. The reversed typical functional segregation phenotype

The persistent identification of participants with completely mirrored functional segregation while probing an increasing number of lateralized functions suggests the existence of a phenotype in which typical functional segregation is generally maintained but in a left/right reversed fashion. If such individuals with mens inversus totalis ('inverted minds') indeed exist[6] it raises the question as to the origin and mechanism of this phenotype. At first glance, reversed typical functional segregation seems difficult to explain by the statistical hypothesis, as it is very unlikely for three or four functions, each having a clear population bias, to be installed in the non-preferred hemisphere if their innate preferences would be independent. On the other hand, if one assumes the existence of an initial symmetry breaking event

[6] This would require confirmed reversal of all lateralized functions, not just a few, and might involve whole brain analysis methods able to explore asymmetries in multiple functional networks. Identifying these individuals would therefore require specialized neuroimaging procedures that extent those for finding people with atypical language dominance.

that results in the reversal of the innate blueprint of typical functional hemispheric organization, then the statistical hypothesis remains a plausible explanation for much of the data. This hypothetical symmetry breaking event[7] happens prior and unrelated to hemispheric differentiation and thus assumes no causal pattern of functional complementarity. Atypical language dominance in left handers would then be secondary to a reversal of general functional segregation in which handedness and language happen to share a similar innate lateralization bias. It does not imply that handedness and language are related. The breaking event would show a prominent population bias towards typical functional segregation, but occasionally give rise to a reversed building plan forming individuals with complete functional reversal, handedness included.[8] A similar mechanism can be proposed for the causal hypothesis, a prior atypical breaking event in which the two unilateral control systems, each innately lateralized to a different hemisphere, get reversed and functional segregation unfolds in a mirrored fashion. It is important to point out that reversed typical functional segregation is not the arbitrator for statistical or causal complementarity as it only assumes (occasional) reversal of the innate biases accepted by both hypotheses. It does not reveal whether these innate biases interact or not. Recognition of different functional segregation phenotypes, however, may eliminate noise from otherwise heterogeneous group data and may give rise to more precise estimations of the association between direction and strength of functional lateralization and thus indirectly contribute to the statistical versus causal complementary dispute.

Whatever the mechanism behind mens inversus totalis, maintained standard functional segregation in individuals with reversed typical functional segregation would predict no neurobehavioral disadvantages in these people. And while one might expect differences in lateralized behavioral tasks in reversed typical participants (such as reversed ear advantages on linguistic and emotional dichotic listening tasks and right pseudo-neglect on line bisection tasks), no differences are anticipated in intellectual, emotional, and artistic capabilities compared to those of individuals with typical functional segregation.[9] Neural responses on the other hand, show mirrored activation patterns in reversed typical functional segregation (but see [11,91] for segregated function pairs using homotopic neural areas) and could at least in part explain frequent reports of less asymmetric brains in left handers when taken as averages over the whole group and disregarding the possibility that they have more heterogeneous brain organization than right handers [7,94].

4.2. The atypical functional segregation phenotype

Different challenges come with the atypical functional segregation phenotype. Its main difference with typical and reversed typical phenotypes is that conventional functional segregation is not maintained and that at least one function is lateralized to an unconventional hemisphere while other function(s) show typical lateralization. Although data is scarce, atypical functional segregation appears more frequently reported than reversed typical functional segregation, is observed in left and right handers, and can be the result of any function lateralizing to the unconventional hemisphere. Why would a function lateralize to a non-preferred hemisphere when all other functions lateralize according to standard organization? As mentioned before, atypical functional segregation is difficult to reconcile with the causal hypothesis unless it is regarded as the consequence of a pathological situation that prevents lateralization of a function to its complementary side. In that case AFS could have behavioral repercussions because normal development would have been disturbed. According to the statistical hypothesis on the other hand, AFS could be the occasional result of an atypically lateralized innate bias of one of the functions. But if functions lateralize independently and there is no specific competition for neural space, crowding should not necessarily give rise to behavioral disadvantage. The claim of a potential behavioral impact of atypical functional segregation is therefore stronger for the causal than for the statistical hypothesis. As outlined above, insufficient evidence is available to favor one or the other prediction.

[7] A similar early breaking event has been proposed for visceral asymmetry to explain cases of SIT that do not have ciliary dysfunction (PCD) [93] Vandenberg LN, Levin M. A unified model for left-right asymmetry? Comparison and synthesis of molecular models of embryonic laterality. Developmental Biology. 2013;379:1–15.

[8] Please note that in this proposal left handedness is regarded a consequence of atypical symmetry breaking. An alternative explanation could be that since rTFS is predominantly seen in sinistrals, genetic mechanisms associated with left handedness increase chances of atypical symmetry breaking and rTFS. Both explanations are not mutually exclusive either.

[9] Unless of course concordance between brain structural and functional asymmetries are behaviorally advantageous in which case rTFS individuals would have a higher risk of incongruent structural and functional lateralization given that both population asymmetries appear largely unrelated.

4.3. To segregate or not to segregate: nuances on complementarity and co-lateralization

A final challenge relates to the concept of complementarity. Functional complementarity assumes a certain degree of specialization minimizing functional overlap and thus redundancy. Similar concepts are used in biology to explain ecological differentiation and biodiversity. When multiple species are specialized and differ in their niche (niche complementarity), interspecific competition is reduced, facilitating co-existence. Functional redundancy in a community on the other hand implies that species are mutually substitutable in terms of an ecological function and that interspecific competition is increased. Transferring this analogy to hemispheric specialization, it may well be that some functions are more complementary to some functions than to others. By this I mean that functions showing high complementarity are more specialized, share less resources, and are more independent of one another (have higher niche complementarity). Linguistic and spatial processing for example are considered fundamentally different functions that have low redundancy in underlying computational processes and neural location [9,48]. Although they typically show functional segregation and occupy a different hemisphere, sharing one is no unusual observation. As high complementary functions do not have to compete for resources in terms of neural space or functional processing, sharing the same hemisphere will not come at an obvious neurobehavioral cost. Functions with low complementarity on the other hand, show less mutual specialization and higher functional redundancy, share more resources, and are more interdependent as they compete for neural space or computational resources. Possible examples are reading and face recognition or linguistic and prosodic speech processing as they process similar perceptual information and rely on roughly homotopic brain regions [95,96]. If this claim is true, then a bias in situations of atypical lateralization should exist toward more frequent hemispheric segregation (and thus reversal of typical functional segregation) for function pairs with low complementarity/high redundancy (as they would compete more for shared resources when in the same hemisphere) that is absent for function pairs with high complementarity/low redundancy which could share a hemisphere (and thus allow for crowding and result in atypical functional segregation) without much competition. In line with this prediction only cases of atypical functional segregation but no cases of reversed typical functional segregation were noted in 75 healthy volunteers assessed for lateralization of language and spatial memory [77], whereas only reversed typical functional segregation but no atypical functional segregation was observed in 73 healthy participants screened for lateralization of linguistic and prosodic processing [12]. In most studies comparing laterality of linguistic and spatial function, higher percentages of atypical than of reversed typical functional segregation are reported [8,75,83]. Although this evidence is circumstantial, it might be relevant to test the assumption empirically in a large sample.

To make things even more complex, some functions like speech and praxis, appear to rely on networks of adjacent and shared regions in the same hemisphere. Lateralization of the activity in these shared nodes appears strongly correlated during speech and praxis tasks and tested RLD participants all show atypical lateralization for both functions suggesting a close link between their neural networks [51]. Speech production and learned manual gestures rely on systematically organized motor output and might have a common evolutionary origin [97,98]. Although language and praxis might compete for neural space in overlapping left hemisphere nodes, their operational 'flowcharts' may be so alike that sharing the network is biologically less costly than creating a separate redundant network in the opposite hemisphere. In the case of language and praxis, hemispheric segregation would predict adverse behavioral consequences. Right hemisphere specialization of functions processing the emotional signal in faces and speech might be another example of a processing system that benefits from hemispheric co-lateralization rather than segregation. There is some evidence that patients with unilateral lesions of the right hemisphere are impaired in labeling emotional expressions from faces *and* voices [99,100], but it remains to be investigated if atypical lateralization of processing one type of emotional stimuli can be independent of the lateralization of processing the other type without behavioral repercussions.

I suggest that both segregation and co-lateralization of function pairs can have advantages dependent on their relation concerning functional and structural redundancy. In terms of statistical versus causal explanations of brain functional segregation this could mean that both models may be right depending on the particular function pair under study. *Statistical* complementarity might better fit high complementarity/less competitive function pairs that share few resources. Evidence for *causal* complementarity on the other hand might be more prevalent in function pairs with low complementarity that would benefit from hemispheric segregation. Evolution has shaped the delicate balance of brain functional organization toward a general blueprint common to most people although variation exists, as our higher cognitive functions do not (yet?) show the more rigid (and highly lateralized) function/structure couplings of

phylogenetic much older primary sensory and motor areas of the brain. Investigating the dynamics and varieties of the ongoing optimization process of functional competition and collaboration may cast further light on the phylogenetic evolution of the human mind and brain.

Hemispheric functional segregation is a promising field of inquiry tapping into the principles of brain organization, its ramifications and potential behavioral consequences. The investigation of hemispheric asymmetries of isolated functions revealed important insights on general human brain organization and its variants. Combining lateralization indices of multiple functions in the same individuals allows further differentiation between phenotypes of typical, or complete (reversed typical) or partial (atypical) reversal of functional asymmetries. Improved identification of these intermediate phenotypes could boost research on descriptive, behavioral, and genetic characteristics that differentiate (or link) with pathological manifestations of atypical hemispheric specialization.

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