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Reply to comment

Toward a multidimensional description of individual variation in hemispheric functional segregation

Reply to comments on “Phenotypes in hemispheric functional segregation? Perspectives and challenges”

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In the target paper, I have provided an integrative and critical view of the current state of affairs regarding hemispheric functional segregation in humans [1]. I have argued in favor of a more comprehensive view on brain organization based on inter-individual differences in functional segregation, which implies investigating relations between lateralized functions rather than asymmetry of a single function. This multifunctional approach enables the identification of phenotypical variation in brain organization and unveils how lateralized brain functions interact (or not), which in turn offers predictions regarding behavioral variation and the origins of human brain organization. I would like to thank all commentators, representing a diverse array of expertise, for their valuable and insightful commentaries, pointing at evidence supporting our framework and raising important challenges of the proposed model and strategy, as well as highlighting open questions in the field of neurobehavioral laterality. Here we discuss some of the important theoretical issues and observations raised by Carey and Karlsson [2], Francks [3], Ocklenburg and Güntürkün [4], Hausmann [5], Thiebaut de Schotten, Friedrich, and Forkel [6], Tzourio-Mazoyer, Zago, and Mazoyer [7], and Vallortigara [8].

1. The problem of measurement

Investigating brain functional asymmetry implies *measurement* of brain functional asymmetry and thus requires the selection and operationalization of representational task paradigms and establishing methods of quantifying laterality. Several commentators have pointed at theoretical and practical issues of measuring functional asymmetry. Hausmann remarks that a clear scientific definition of typical (language) lateralization does not exist [5]. Does an fMRI-derived laterality index of .65 based on activated voxels in favor of the left Broca area during a word fluency task reflects typical language lateralization? Yes and no. Yes, because this coefficient reflects the population standard on this type

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of language task [9] and predicts aphasic symptoms in validation studies applying temporary perturbations (sodium amytal test, TMS) over the left hemisphere [10,11]. No, because word fluency is merely one task to assess only one (productive) aspect of language and thus should not be used to represent ‘language’ as a whole. Moreover, Broca’s region is just one node of the verbal fluency network and does not necessarily represent lateralization of the other network hubs [12]. Hausmann also points at factors that give rise to dynamic changes in lateralization state, such as hormonal fluctuations or age. Indeed, many factors influence the assessment of a function’s laterality, from the trait-like asymmetry bias specific to the selected task, over dynamic fluctuations, to pure measurement error. Carey and Karlsson [2] remind us of the paucity in validity and reliability studies on measures of laterality, an issue that should be addressed duly if we aim to use the laterality spectrum at the level of the individual [13,14]. Which brings us to the issue of categorization based on seemingly arbitrary cutoffs of ‘hemispheric dominance’ to perform group comparisons and whether or not to include a ‘bilateral dominance’ category, an approach embraced by some, distrusted by others and which also awaits recommendations from test-retest reliability studies [2].

Despite the list of caveats in measuring functional specialization forwarded in the comments, neuropsychological and neuroimaging research also revealed robust mechanisms that support current methodological choices even if they do not take the full complexity of the functional network into account. Most linguistic functions co-lateralize to the same (left) hemisphere in the human population, as do the core hubs within each linguistic network (but see [15]). This also holds for motor control whether it be on the semantic (praxis) or executive (handedness) end of the spectrum.[1] Spatial functions on the other hand prefer the right hemisphere when probed by spatial tasks of attention, memory, or reasoning [16] and similar right hemisphere preference is observed for perception of emotion whether expressed by speech or face. Although we can debate on the best representative task and explore asymmetry differences between subcomponents of language or spatial behavior, it is clear that the main characteristics of hemispheric functional segregation are quite straightforward, as is also advanced by Thiebaut de Schotten et al. [6]. And while trait-like asymmetries may be influenced by state-like fluctuations, my clinical background reminds me that most patients with left inferior frontal strokes present with symptoms of non-fluent aphasia, regardless of their age or period of menstrual cycle. Without ignoring the complexity and dynamics of what we are trying to measure, lesion studies have provided essential observations concerning hemispheric specialization that should inspire task selection. We cannot measure the laterality of ‘language’, but we can measure hemispheric asymmetry in key hubs of principal language components that have demonstrable neural basis. Analysis of the neural activation patterns induced by clinically inspired task paradigms in sufficiently large groups of healthy participants will result in phenomenological description of normal variation and finally lead to consensus on what the typical neural activation pattern of a given paradigm looks like. For many cognitive tasks this information is not yet available, and even in the realm of language, probably the best studied asymmetric function, we are merely scratching the surface. When collected, these data might offer evidence-based criteria for defining cutoffs for classification or, alternatively, the findings may reveal that classifications are pointless. Either way, we will need this information to guide future research.

Establishing phenotypical variation in the asymmetry of activation patterns for several key paradigms will provide an important stepping stone for the understanding of functional segregation and its behavioral correlates and I completely agree with Hausmann that looking at the laterality of one function in itself is not very informative regarding performance [5]. This is exactly why I argue for a more comprehensive approach of brain organization that takes the within-subject interaction between lateralized functions into account and may turn out to be a better predictor of performance differences or even pathology than a single laterality score. Which brings me back to this section’s topic: how do we measure this relation? One option would be to compare an individual’s activation pattern against the population standard and use difference scores to predict behavior [17], other methods based on network science and graph theory can be explored as well [18]. With attempts to understand the biological roots of human brain organization still in its infancy, measuring variation and impact of functional interaction awaits new ideas and refinement.

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[1] Here, handedness is considered just another lateralized function in the human brain. Because handedness is so easy to assess, its neural correlates remain underexplored compared to other functions that require more elaborate methods to assess hemispheric dominance. Why not determine a laterality index for handedness based on the neural response during manual fine-motor performance just like we do for the other functions, and use this LI to explore between-functional relations and coherence with motor performance asymmetries? This approach would place handedness on the same level of measurement (with all its pro’s and con’s) as functions with less behaviorally apparent asymmetry.

2. Determining the optimum level of neurobiological description

Francks proposed three main research goals to advance our understanding of typical and atypical developmental mechanisms of human brain asymmetry [3]. In addition to identifying the complex genetic-developmental cascade of typical asymmetry as well as the heterogeneity of developmental causes of atypical lateralization, he argues that we need to establish an optimum level of neurobiological description to capture the phenomenon of functional brain asymmetry and that the current measures of neuroimaging may not be sufficient to describe 'crowding' or 'dominance' in the fine-tuning of neuronal network properties. As things stand, conventional non-invasive neuroimaging is not able to contribute to the cell and circuit level of the cell-circuit-network-function relations Francks is referring to and would require important technical advances. The importance to reach deeper levels of neuronal understanding and the relevance of animal research in this respect is also mentioned by Ocklenburg and Güntürkün [4] who advocate a comparative perspective toward the biology of hemispheric specialization, whereas Thiebaut de Schotten et al. [6] mention across species comparison useful for insights into the evolution of brain asymmetry.

As mentioned in the previous paragraphs, many methodological issues with laterality measures remain to be solved, but at least regarding magnetic resonance imaging I am optimistic that we can significantly improve the level of neurobiological description to inform research. Instead of using massively aggregated or highly selective neuronal activity to establish a function's asymmetry, the adoption of a strategy that focuses on key hubs of a function's network would certainly offer a more fine-grained picture of functional asymmetry and within-network variability. Word generation paradigms, for example, activate a widespread lateralized network of cerebral (and cerebellar) activation, but laterality indices are usually calculated over Broca's region only, which leaves a lot of data regarding within-network asymmetry unused. Recent advances in the imaging and quantification of white matter and in connectivity analysis methods of structural and functional imaging add to the growing toolbox that enables a more detailed description of brain asymmetry. Classic laterality indices will remain very informative in laterality research but gearing up towards a multidimensional and network-level description of phenotypes in human brain asymmetry is certainly within our reach.

3. Issues of phenotyping

A phenotype is the set of observable characteristics or traits of an organism and the result of its genetic code, environmental influences, and their interaction. Ocklenburg and Güntürkün draw our attention to the importance of environmental factors in the ontogenesis of hemispheric asymmetries [4]. They underline the interplay of genetic and environmental influences in the formation of various asymmetry phenotypes and point at the lack of systematic research covering the envirotype-side of the spectrum. Ocklenburg and Güntürkün also mention the relevance of animal research for the investigation of environmental factors on brain functional asymmetries. I fully agree on raising awareness for environmental factors and this research could also benefit from the multifunctional approach advocated in the target paper in which environmental effects on relations between asymmetric functions are considered. A multifunctional approach then, could inform researchers on the possibility of environmental factors co-influencing lateralization of multiple traits proposed by the commentators [4].

In the target paper I proposed the existence of at least three phenotypes of hemispheric functional segregation that have theoretical relevance to improve understanding of the mechanisms underlying human brain asymmetry. Several commentators have argued that the proposal of three phenotypes falls short of the anticipated heterogeneity of inter-individual functional segregation [5,6]. I agree with this remark, but the limited amount of available data did not allow a more fine-tuned proposal of phenotyping, hence the three broad categories of typical, reversed typical, and atypical functional segregation. By probing an increasing amount of lateralized functions in the same individuals, we might have to conclude that typical functional segregation does not exist and that there is an infinite number of phenotypes. Alternatively, it can be argued that there is just one basic type of hemispheric functional segregation with minor variants of accidental reversal or failure to achieve prototypical brain organization. Before embarking on more detailed phenotyping, we will first have to make a better description of inter-individual variability in functional segregation and its behavioral correlates. It would be informative to see if atypical lateralization is truly random (is observed for all functions with the same frequency), or whether some patterns are more frequent than others while some don't seem to occur at all. This approach should be substantiated by previous findings with regard to dominance-patterning as suggested by Tzourio-Mazoyer et al. [7] and should be extended to atypical lateralization of other functions besides language as pointed out by Carey and Karlsson [2]. I agree with Thiebaut de Schotten et al. [6]

that characterizing phenotypes could have clinical relevance with regard to recovery after brain damage, identification of biomarkers predicting lateralization and segregation, and personalized medicine.

4. Behavioral correlates of crowding

Apart from people with completely mirrored functional segregation, atypical lateralization of a function will result in crowding as a hemisphere will have to store both its usual and the novel functions. In healthy participants crowding is generally regarded a deviation from the ideal scenario, although its behavioral repercussions remain unclear. In some instances crowding is reported to be behaviorally advantageous [19], but several commentators acknowledge possible drawbacks of crowding which is observed in roughly 20% of the population [2,3,8]. Although I do not agree with Tzourio-Mazoyer et al. [7] that cases of crowding in healthy individuals are merely the result of whole brain averaging and reflect measurement error rather than reality, I fully concur with their proposal to construct an operational definition of crowding that should be based on targeting the lateralization of core hubs activated by standard paradigms that represent key cognitive functions.

To better explain the divergent behavioral correlates of crowding I elaborated on effects of complementarity and co-lateralization. High complementary functions have neural and computational independence and atypical hemispheric lateralization of one function will not interfere with the other. Word production and spatial attention are high complementary functions (as demonstrated nicely for the neural pattern in Figs. 1C and D of the comment of Tzourio-Mazoyer et al. [7]), and their crowding is expected to have little if any behavioral effect. Low complementary functions on the other hand, like word-form perception and face perception compete for neural and computational resources and crowding is more likely to be associated with adverse performance [20]. Besides complementarity, co-lateralization is another factor to consider when estimating the behavioral correlates of atypical lateralization. By co-lateralization I mean the tendency of functions to be represented in the same hemisphere and share (parts of) their network thereby avoiding redundancy and excessive interhemispheric transfer. Many language functions show co-lateralization, as do spatial functions or functions underlying motor behavior, but also functions that do not seem related at first sight like praxis and language production [12]. Co-lateralized function pairs may impact behavior when they become segregated in different hemispheres. Take the example mentioned by Carey and Karlsson who noted the paradoxical hemispheric segregation of hand preference and praxis dominance in nearly 80% of left handers [2]. It can be argued that such an unconventional organization of the motor behavior network might be disadvantageous under certain circumstances or would require significant compensatory neural adaptations that would distinguish atypical from typical individuals. The atypical segregation of language and praxis dominance could be associated with similar observations of suboptimal performance or neural adaptations. It remains to be determined under what circumstances crowding has measurable behavioral correlates. Both Francks [3] and Ocklenburg and Güntürkün [4] have rightly referred to the flexibility and plasticity of neuronal circuits implying an ability to ‘buffer’ or accommodate effects of crowding. Vallortigara [8] on the other hand suggested that some asymmetries may not produce any bias in overt behavior and therefore fitness. I hope we can agree on the idea that crowding is not by default associated with adverse behavioral effects (or psychopathological consequences). And that potential behavioral correlates depend on the level of complementarity and co-lateralization with functions required for task performance that surpass the habitual capacity of neuronal circuits to compensate for alternative network configurations. To further our understanding of the implications of altered functional asymmetry it is of paramount importance to complement measures of functional segregation with measures of behavior.

5. Biology of hemispheric functional segregation

Francks underlines the massive heterogeneity in genetic, environmental, and chance mechanisms that lead to atypical brain asymmetry and warns that this causal heterogeneity may defy attempts to classify phenotypes into etiological categories [3]. This is a fair point and other commentators have raised similar caveats that may obfuscate a full understanding of the variation in functional segregation including state-dependent influences on laterality [5]. On the other hand, we cannot deny the fact that the majority of the population shows prototypical functional brain asymmetry despite the myriad causes for perturbation and that there is some order in the chaos of asymmetric developmental processes. Identification of people with typical brain organization as evaluated by a multidimensional approach can at least exclude or downplay the impact of alleged influencers of human brain asymmetry. I am not suggesting that the interplay of genetic and non-genetic mechanisms of brain asymmetry will be an easy puzzle, but it can be anticipated that at least some of its perturbations will have a definable cause. In order to identify such causes, we need a better description of adult variation in brain functional segregation complemented with genetic information and detailed environmental data on variables reported to influence lateralization. Take people with reversed typical functional segregation for example. It seems likely that such a substantial rearrangement occurs very early in development, perhaps as a consequence of atypical left-right axis determination (but see Vallortigara [8]). Point is that such fundamental perturbations can be powerful phenotypes to investigate its underlying causative mechanisms whether genetic or environmental in origin. Not many phenotypes will be that spectacular however, and we will have to investigate large samples of participants to describe the full spectrum of phenotypical variation: From partial atypicalities affecting fewer functions or reducing (rather than reversing) laterality strength to a complete break-down of typical functional segregation and co-lateralization between or even within the network-level. Here, frequency of occurrence and behavioral correlates may be informative for the etiology of these modifications and more subtle atypical arrangements are more likely to result from a combination of factors.

Vallortigara [8] draws our attention to the mystery of population level asymmetry. While several plausible arguments favoring hemispheric asymmetry over hemispheric symmetry can be offered, it has proven far more difficult to explain why the majority of the population shows exactly the same pattern of left/right functional segregation that we refer to as ‘typical’. According to Vallortigara, the answer to this crucial question is the need for asymmetrical organisms to coordinate their behavior with that of other asymmetrical organisms and give rise to an evolutionary stable strategy. He provides several examples from the animal world that appear plausible but may not apply to the human species. It might be challenging to think of a reason for population level alignment of left hemisphere language dominance for example, unless language asymmetry is linked to the asymmetry of other functions that may have more obvious advantages of population level alignment, which makes another argument to investigate between-functional relations of asymmetry. Vallortigara deems the existence of a phenotype with complete mirror reversal of typical functional segregation likely, as these individuals will have the same fitness advantages as typical individuals, but he predicts this variation to be a minority because of the selection pressure toward behavioral alignment at the population level. Regarding atypical functional segregation (crowding) he agrees with our view that crowding may bring (occasional) disadvantage and forwards the interesting idea that minority phenotypes may have frequency-dependent advantage for a single task, but whose arrangement would at the same time be disadvantageous for a combination of tasks. I agree with Vallortigara [8] that strategically selected dual tasks provide the best opportunity to evaluate the link between crowding and performance.

6. Future research

Despite the many challenges that await researchers of brain laterality and which have been outlined in the commentaries and in this rebuttal, there is also a sense of optimism that the field is in position to engage in efforts describing hemispheric functional segregation at the phenotype level. Carey and Karlsson [2] predict a bright future for the study of multiple cerebral asymmetries, Thiebaut de Schotten et al. [6] suggest to join efforts and construct a consortium to create a multidimensional database on brain asymmetry, and other commentators agree the time is ripe for large scale research efforts exploring individual variation in functional human brain asymmetry [2,3,6,7]. I sincerely hope that the exchange of ideas provided here by the format of Physics of Life Reviews will inspire other researchers as well and may contribute to future collaborative research on human brain laterality. Measuring asymmetries of multiple functions in the same individuals and reporting individual data on the laterality spectrum complemented with genetic and environmental data in association with behavioral performance data of the investigated functions appears to be a sensible way forward.

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