Available online at www.sciencedirect.com

ScienceDirect

Physics of Life Reviews 30 (2019) 34–37

PHYSICS of LIFE reviews

www.elsevier.com/locate/plrev

Comment

What can we learn from healthy atypical individuals on the segregation of complementary functions? Comment on “Phenotypes in hemispheric functional segregation? Perspectives and challenges” by Guy Vingerhoets

Nathalie Tzourio-Mazoyer *, Laure Zago *, Bernard Mazoyer

Groupe d’Imagerie Neurofonctionnelle, Institut des Maladies Neurodégénératives-UMR 5293, CNRS, CEA, University of Bordeaux, Bordeaux, France

Received 10 September 2019; accepted 11 September 2019
Available online 13 September 2019
Communicated by J. Fontanari

In this comment, we would like to emphasize three important points discussed in the remarkable synthesis conducted by Guy Vingerhoets on the neural bases of hemispheric specialization (HS).

How many types of hemispheric dominance exist in healthy individuals?

In the first part of his review [7], Guy Vingerhoets underlines that the term “atypical” for language includes two different groups of individuals, those having a mirrored representation of language with a right hemispheric dominance for language, and those with no hemispheric lateralization, considered as having a bilateral language representation. We strongly agree with this notion and would like to go one step further in the description of these types of atypical lateralization. Actually, weak or non-significant asymmetry as measured with functional imaging during language tasks can result from very different hemispheric patterns of brain activity. For example, in [6], atypical individuals exhibiting low asymmetry during language production (ambilaterals) were actually of different types: the first type included Right-Handed (RH) individuals who showed decreased left hemisphere activation and increased right hemisphere activation as compared to typical individuals; the second type included Left-Handed (LH) individuals that showed strong and bilateral activations. Interestingly, we also observed that the strength of inter-hemispheric temporal correlation of the resting state BOLD signals was higher in these LH ambilaterals than in any of the other groups of hemispheric lateralization, indicating a different brain organization, probably with more cooperation and/or less inhibition across homotopic language regions.

Nevertheless, this last study did not address the status of each hemisphere in each individual showing a comparable recruitment of language regions in the two hemispheres. For example, having two dominant hemispheres for language could correspond to the notion of ambilaterality as defined by Hécaen, with two hemispheres competent for language which could lead to better recovery in case of lesion [1]. But bilateral activations could also correspond to an absence of any dominant hemisphere as previously evidenced by Wada testing in epileptic patients. In particular, Möddel et

DOI of original article: https://doi.org/10.1016/j.plrev.2019.06.002.

* Corresponding authors.
E-mail addresses: nathalie.tzourio-mazoyer@u-bordeaux.fr (N. Tzourio-Mazoyer), laure.zago@u-bordeaux.fr (L. Zago).

https://doi.org/10.1016/j.plrev.2019.09.003
1571-0645/

al.'s report demonstrates the existence of ambilaterals having two hemispheres dominant for language and that of individuals with two hemispheres non-dominant for language (meaning that the anaesthesia of either hemisphere did not result in any language deficit; [3]). We investigated this issue using a support vector machine (SVM) method for classifying each hemisphere as either dominant or non-dominant in each ambilateral individual. We first trained the SVM algorithm on the right (non-dominant) and left (dominant) hemisphere of 250 typical individuals [4] and then applied the SVM algorithm on the groups of atypical individuals [8]. We demonstrated that all RH individuals had a left hemisphere classified as dominant, together with, in a few cases, a right hemisphere also classified as dominant (leading for these individuals, to a co-dominant pattern). By contrast, LH individuals exhibited a high variability, including left dominance, right dominance, co-dominance (two dominant hemispheres) and co-non-dominance (two non-dominant hemispheres).

Because SVM approach is based on the intra-hemispheric pattern of activation independently in each hemisphere, the co-dominant and co-non-dominant individuals are also characterized by their leftward, rightward or absence of functional asymmetry leading to numerous types of atypical organization. A fine-grained definition of the existing types of language lateralization should thus take into account both the inter-hemispheric pattern, measured with task-induced hemispheric asymmetry indices (HAI), and each hemisphere's dominance pattern measured at the voxel level.

Does crowding actually exist in healthy individuals?

The location within the same hemisphere of the regions dominant for two different cognitive functions, usually split across hemispheres, is supposed to be the cause of non-optimal cognitive functioning in pathological states. But one can wonder whether such a co-location exists in healthy individuals. Actually, in most studies, the definition of crowding is based on asymmetry indices (AI) averaged on the whole hemisphere. In such cases, the fact that AI have the same sign does not mean that the core areas dominant for each function overlap. For example, as seen in Figure 1 (Atypical functional segregation: C and D), the BOLD activity maps of the two individuals exhibiting leftward or rightward HFLIs for both language production and spatial attention do not evidence overlapping brain regions within the dominant hemisphere, suggesting that the division of cognitive functions is respected within the hemisphere. We think that an operational definition of crowding is needed to interpret the hemispheric co-lateralization including the consideration of (1) both hemispheric and regional asymmetries; (2) both asymmetries and BOLD variations; (3) the targeting of core regions and/or networks involved in each cognitive function. Fulfilling those conditions will allow to attest whether or not crowding exists in healthy participants and if so to investigate its possible impact on cognitive performances.

Variability of complementary hemispheric specialization is a key for deepening our understanding of the setting of hemispheric specialization.

For some authors, complementary hemispheric specialization is the outcome of an evolutionary scenario that allowed the development of cognitive functions and the emergence of language [2]. The split of functions across hemispheres may also be the result of a developmental step in the inter-hemispheric setting-up of complementarity. Whether this complementarity is causal or statistical cannot be decided on the basis of correlation analysis since correlation is not causality. Rather, such correlation between complementary functions across individuals should be viewed as indexing the variability in patterns of inter-hemispheric organization. For instance, we demonstrated that while there was no association between spatial and language HAI in RH, LH exhibited a significant negative correlation: the stronger their language lateralization in one hemisphere, the stronger their rightward visuo-spatial lateralization in the contralateral hemisphere [9]. Such an observation prompts for widening the research on HS through the characterization of the various types of organization of lateralization of different complementary cognitive functions.

Acknowledgements

We are deeply indebted to all colleagues of our research team that contributed to the design, acquisition, analysis and valorisation of the BIL&GIN, a database dedicated to the study of hemispheric specialization, namely: L. Petit, M. Joliot, E. Mellet, G. Jobard, and a special thank you to the engineers that supported us: M. Vigneau, N. Delcroix, F. Lamberton, M.-R. Turbelin, G. Leroux and G. Perchey.

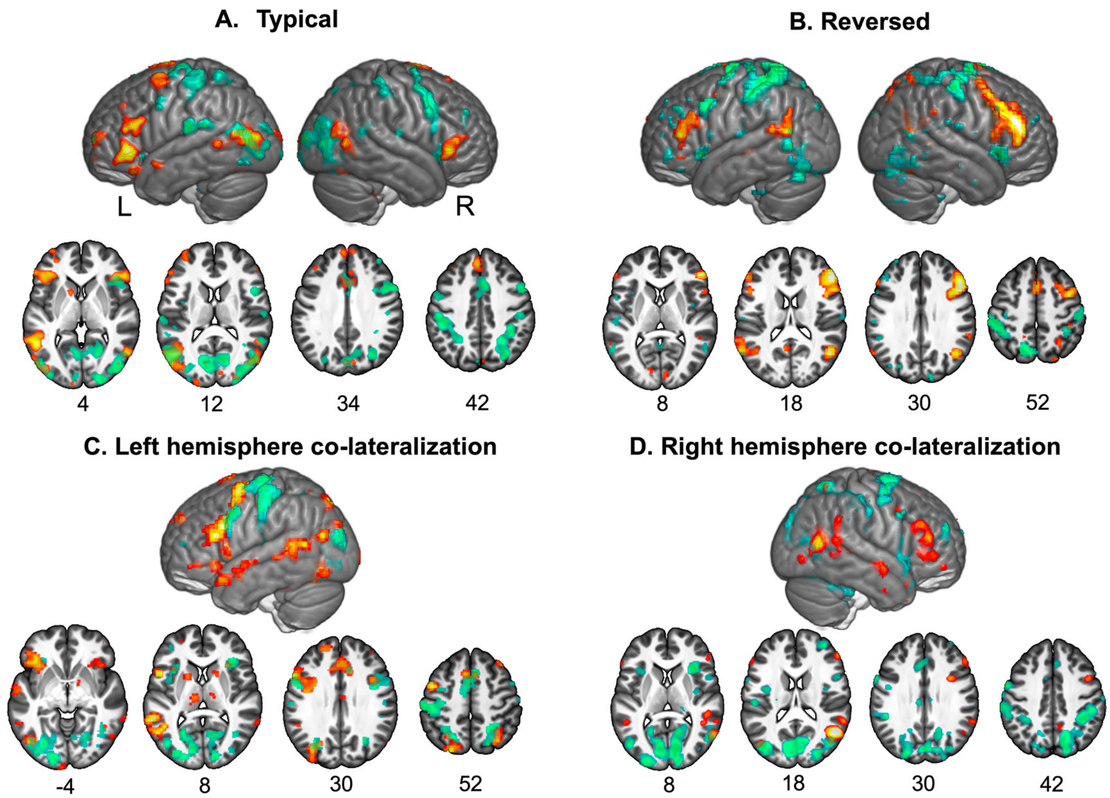

Fig. 1. **Individual BOLD contrast maps illustrating at the voxel level different *"phenotypes in hemispheric functional segregation"* described by Vingerhoets for language and attention** [7]. These four types were based on Hemispheric Functional Laterality Index (HFLI) measured during language production (Production of sentences *vs.* Production of words lists, PROD, hot colours) and spatial attention (Line bisection Judgement -LBJ- *vs.* Fixation, cold colours). **A. Typical pattern of functional segregation**: This right-handed man exhibited HFLIs that were leftward for language ($HFLI_{PROD} = +54$) and rightward for attention ($HFLI_{LBJ} = -44$). Such a typical complementary pattern corresponds regionally to larger BOLD activity in the left frontal and temporal regions during language production, and to larger activity in the right inferior occipito-temporal regions, intraparietal sulcus, and precentral gyrus/middle frontal gyrus during LBJ. **B. Reversed pattern of typical functional segregation**: This left-handed woman exhibited a rightward HFLI for language ($HFLI_{PROD} = -72$) and a leftward HFLI ($HFLI_{LBJ} = +65$) for attention. Regionally, larger BOLD activity can be seen in right fronto-temporal regions for language and larger BOLD activity in the left superior/intraparietal parietal areas for attention. **C. Atypical functional segregation: crowding in the left hemisphere**: This left-handed woman exhibited leftward HFLIs for both language and attention ($HFLI_{PROD} = +57$; $HFLI_{LBJ} = +43$). Typical left regional activation pattern for language can be seen while larger BOLD activity is observed during LBJ in the left inferior occipito-temporal regions. Importantly, there is no overlap of BOLD activation for the two functions, except in the lower part of the anterior insula/inferior orbital frontal gyrus and pre-SMA related to executive aspects involved in both tasks. **D. Atypical functional segregation: crowding in the right hemisphere**: This left-handed woman exhibited rightward HFLIs for both language and attention ($HFLI_{PROD} = -65$; $HFLI_{LBJ} = -20$). The rightward asymmetry is obvious in the inferior frontal gyrus and temporal areas during language production, while larger BOLD activity during LBJ is mainly observed all along the right intraparietal sulcus. Note again the absence of overlap within the right hemisphere. Individual maps are displayed on a template of the BIL&GIN database [5]. Note that participants responded with their right-hand and that the motoric response is subtracted by the language production contrast but not during LBJ that is compared to cross fixation.

References

[1] Hécaen H, Sauguet J. Cerebral dominance in left-handed subjects. Cortex 1971;7:19–48.
[2] Hutsler JJ, Gillespie ME, Gazzaniga MS. The evolution of hemispheric specialization. In: Caliassano P, Volterra V, editors. The evolution of hemispheric specialization. New York: Academic Press; 2002. p. 37–49.
[3] Möddel G, Lineweaver T, Schuele SU, Reinholz J, Loddenkemper T. Atypical language lateralization in epilepsy patients. Epilepsia 2009;50:1505–16.
[4] Mazoyer B, Zago L, Jobard G, Crivello F, Joliot M, Perchey G, et al. Gaussian mixture modeling of hemispheric lateralization for language in a large sample of healthy individuals balanced for handedness. PLoS ONE 2014;9:e101165.
[5] Mazoyer B, Mellet E, Perchey G, Zago L, Crivello F, Jobard G, et al. BIL&GIN: a neuroimaging, cognitive, behavioral, and genetic database for the study of human brain lateralization. NeuroImage 2016;124:1225–31.

[6] Tzourio-Mazoyer N, Joliot M, Marie D, Mazoyer B. Variation in homotopic areas' activity and inter-hemispheric intrinsic connectivity with type of language lateralization: an FMRI study of covert sentence generation in 297 healthy volunteers. Brain Struct Funct 2016;221:2735–53.
[7] Vingerhoets G. Phenotypes in hemispheric functional segregation? Perspectives and challenges. Phys Life Rev 2019;30:1–18. https://doi.org/10.1016/j.plrev.2019.06.002 [in this issue].
[8] Zago L, Hervé PY, Genuer R, Laurent A, Mazoyer B, Tzourio-Mazoyer N, et al. Predicting hemispheric dominance for language production in healthy individuals using support vector machine. Hum Brain Mapp 2017;38:5871–89.
[9] Zago L, Petit L, Mellet E, Jobard G, Crivello F, Joliot M, et al. The association between hemispheric specialization for language production and for spatial attention depends on left-hand preference strength. Neuropsychologia 2016;93:394–406.