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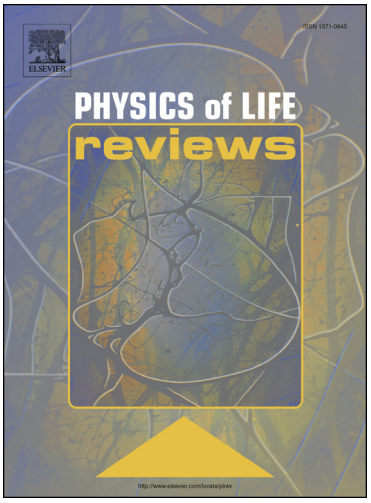

In search of the biological roots of typical and atypical human brain asymmetry

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In search of the biological roots of typical and atypical human brain asymmetry.

Comment on "Phenotypes in hemispheric functional segregation? Perspectives and challenges" by Guy Vingerhoets.

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In this comprehensive and insightful review, Vingerhoets [1] discusses the multi-dimensional nature of inter-individual variation in functional brain asymmetry, and its potential relevance to behavioural variation and psychopathology. Some key points that emerge are: a) most individuals show a stereotypical pattern of hemispheric functional segregation, but non-typical variants are also relatively common in the population, b) different functional asymmetries vary largely, but not wholly, independently of each other, c) complete left-right mirror reversals affecting many functions are found in a small minority of people, but more commonly only some of the functional asymmetries are altered, and by degree rather than fully reversed, and d) the literature suffers from many small-scale studies that have yielded statistically ambiguous results, including on behavioural associations with rearrangements of functional asymmetry.

Here I would like briefly to stress three research goals, on which I expect Vingerhoets will agree. First, we need to identify the genetic-developmental mechanisms underlying typical functional asymmetry in the majority of people. Second, we need to anticipate the likely heterogeneity of developmental causes of atypical functional asymmetry, and start to identify some of them. Third, we need to find the optimum level of neurobiological description to capture the phenomenon of functional brain asymmetry. These three goals are intertwined. If achieved, then it will also become clearer why some forms of altered functional asymmetry are linked to behavioural and psychopathological consequences, and others not.

The core developmental mechanisms for human brain asymmetry are unknown [2, 3]. However, such mechanisms have been described for asymmetrical patterning of the vertebrate visceral organs (heart, lungs, etc.) [4, 5], as well as for asymmetry of fish brains [6]. Various lines of evidence suggest that the specific mechanisms identified so far have limited relevance to human brain asymmetry [2, 6-11], but nonetheless they have taught us some important principles. We have learned that innate chirality (handedness) of biomolecules can trigger the formation of a left-right axis in early embryonic development [12, 13]. Importantly, once the direction of the axis is established, complex developmental cascades then come into play, involving many different genes activated differently on the two sides in precise spatiotemporal patterns, that ultimately give rise to the adult asymmetrical form [6].

In contrast, for human brain asymmetry, the field is only just starting to identify some of the genes involved, thanks to a new generation of genetic association studies based on sample sizes of tens or hundreds of thousands of individuals [8, 14, 15]. Most of the earlier findings were based on poorly powered genetic association studies [2, 8], but the field is now positioned to move forward in a solid way. It is too early to tell whether the kinds of biological processes involved in, for example, patterning the brain for hand dominance are different to those for language dominance, although preliminary evidence suggests that this might be the case [3, 16]. Importantly, it is currently unclear whether any of the individual genes identified so far point to core developmental mechanisms for patterning the left-right brain axis, or whether they are peripheral modifiers of the eventual adult outcome.

The intricacy of asymmetrical developmental processes means that they can be perturbed in a very large number of ways. For example, mutations in at least 50 different genes lead to altered visceral laterality in humans [17], which can be anything from complete mirror reversals of all visceral organs, to restricted disruptions of individual organs. By analogy, as Vingerhoets [1] and others [16] have argued, people who have full mirror reversals of multiple functional brain asymmetries may have undergone very early developmental rearrangements, that altered the initial direction setting of the brain's left-right functional axis for many domains. Whereas partial rearrangements that affect a smaller number of specific functions, often involving reduced rather than reversed asymmetry, might arise from influences later in development, affecting a more restricted set of brain regions or networks. Yet other disruptions might lead to a loss of developmental canalization of asymmetry, such that variability increases, and the typical relations between different asymmetrical functions break down.

As things stand, we barely understand the genetic, environmental, and chance mechanisms that cause atypical human brain asymmetrical development [2, 3, 18]. However, given the complexity of development, we can anticipate a high degree of causal heterogeneity leading to the range of different alterations of functional laterality in the population. Such causal heterogeneity may defy our best attempts to classify phenotypes of hemispheric functional segregation into a limited number of etiological types, although efforts to classify at the phenotypic level should certainly be pursued, and may help to pinpoint underlying causes. It would also then become clearer which causes have behavioral or psychopathological consequences, and whether asymmetry itself mediates these associations in some cases.

Regarding the optimal neurobiological level of description, then the field is largely limited to non-invasive, indirect measures of massively aggregated neuronal activity, such as provided by functional magnetic resonance imaging. This may not be sufficient to resolve whether, for example, within-hemisphere functional crowding occurs, when one hemisphere becomes dominant for functions that are usually lateralized to opposite hemispheres. There needs to be a step change in our understanding of cell-circuit-network-function relations and dependencies, which will likely require both technical and computational advances, and invasive work with animal models. I agree with the insight by Vingerhoets [1] that some functions are likely to have 'operational flowcharts' that are alike, and could then be well supported by overlapping brain networks with particular information-processing properties. One of the attractive features of research on brain asymmetry is that it involves a natural contrast between two closely alike hemispheres, where the key differences are likely to be in the fine-tuning of neuronal network properties [19]. If we can identify the genetic

basis for this fine-tuning, and the expected myriad of heterogeneous genetic, and non-genetic, causes for its perturbation in some people, then we will be closer to understanding the phenotype and its associations.

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