

Comment

One size fits all does not apply to brain lateralisation

Comment on “Phenotypes in hemispheric functional segregation? Perspectives and challenges” by Guy Vingerhoets

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Our understanding of the functioning of the brain is primarily based on an average model of the brain's functional organisation, and any deviation from the standard is considered as random noise or a pathological appearance. Studying pathologies has, however, greatly contributed to our understanding of brain functions. For instance, the study of naturally-occurring or surgically-induced brain lesions revealed that language is predominantly lateralised to the left hemisphere [1] while perception/action and emotion are commonly lateralised to the right hemisphere [2,3]. The lateralisation of function was subsequently replicated by task-related functional neuroimaging in the healthy population [4–6]. Despite its high significance and reproducibility, this pattern of lateralisation of function is true for most, but not all participants. Bilateral and flipped representations of classically lateralised functions have been reported during development [7–10] and in the healthy adult population for language [11], perception/action [12] and emotion [13]. Understanding these different functional representations at an individual level is crucial to improve the sophistication of our models and account for the variance in developmental trajectories, cognitive performance differences and clinical recovery. With the availability of *in vivo* neuroimaging, it has become feasible to study large numbers of participants and reliably characterise individual differences, also referred to as phenotypes. Yet, we are at the beginning of inter-individual variability modelling, and new theories of brain function will have to account for these differences across participants [14].

Within this context, Guy Vingerhoets argues in his review [15] that three main phenotypes of functional lateralisation prevail: The *order* type corresponds to the common pattern of lateralisation, where language functions are dominant in the left, while perception/action and the processing of emotional stimuli are dominant in the right hemisphere. The *reverse* type corresponds to a “flipped” pattern, with language being dominant in the right and per-

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ception/action and emotion in the left hemisphere. Lastly, in the *crowded* type, functions that are usually dissociated between the two hemispheres, are co-located within the same hemisphere. In healthy controls, the *order* and *reverse* types have a small general cognitive advantage on standard neuropsychological assessments [16,17], whereas the *crowded* type may be advantageous in some situations. For instance, a strong dominance of attention in the right hemisphere in left-handers combined with a right eye dominance has been suggested as a critical advantage for sporting duels [18].

Two hypotheses may explain the existence of a *crowded* type. The pathological hypothesis suggests that the *crowded* type is associated with an interrupted or disturbed development of functional lateralisation [19], which manifests with a small cognitive disadvantage. The evolutionary hypothesis, on the other hand, suggests that the *crowded* type is a normally developing phenotype that thrives in specific situations and hence survived through evolution. While genes, handedness, gender and *situs invertus* have been shown to have a minimal association with lateralisation types (see Vingerhoets et al. [15] for an extensive review), lateralisation phenotypes are critical in the presence of brain damage and may determine the potential for the recovery of function (e.g. language recovery [20,21], visuospatial neglect recovery [22]). *Crowded* or *reverse* functional lateralisation is evident in numerous neurodevelopmental and psychiatric conditions [23], including a stronger right lateralised attention network in attention deficit hyperactivity disorder [24] and a weaker left lateralisation of language networks in autism [25] and schizophrenia [26]. Whether this lateralisation causes or is contingent to psychiatric conditions remains to be clarified [19]. This body of literature may suggest that functional lateralisation has been finely tuned across millions of years of evolution, and characterising these phenotypes is critical to advancing personalised medicine.

How does one accurately decipher the phenotypical organisation of the lateralisation of brain functions? Studying brain lateralisation has been hampered by various limitations, including the sometimes shallow relationship between structural and functional asymmetries [27], the low replicability of behavioural, functional and anatomical measures and the often small group sizes. Guy Vingerhoets suggests that a comprehensive model of the lateralisation of brain functions will require a high-dimensional, rather than a uni- or bidimensional approach [28], to capture the complementary trade-off or independence between lateralisation in behavioural measures, functional brain activations, brain anatomy, and their relationship with genetic data across a large subsample of the population. At the dawn of the open science/open data revolution, this endeavour seems feasible and timely, as preliminary evidence recently demonstrated for structural lateralisation [29]. The high-dimensional analysis of brain lateralisation will allow for the demonstration of the existence and the origin of an entirely reverse type; indicate whether *order*, *reverse* and *crowded* phenotypes are truly segregated or part of the same continuum; potentially reveal other phenotypes (i.e., is partially crowded possible?), and identify predictive biomarkers for brain lateralisation that will subsequently be translated to the clinic. It will also allow enable the objective testing of whether separate and overlapping Gaussian distributions are hidden behind brain lateralisation [30] and will lead to new hypotheses on mechanisms supporting functional lateralisation and recovery after brain damage [31]. A preliminary hypothesis proposed by Guy Vingerhoets [15] amongst other authors [32,33], would be that function is lateralised in the brain in order to minimise functional overlap and redundancy, and thus enhance cognitive capacities. Accordingly, functional segregation across the hemispheres and the co-lateralisation of function can be advantageous or disadvantageous according to whether they rely on redundant processes. Such explorations will help one understand the functioning of the brain and elucidate some of the evolutionary mechanisms that support functional specialisation and segregation. This is in line with preliminary evidence that suggests that variability may be a significant landmark of recent evolutionary trends [34] and might impact limbic functions (e.g., emotion) differently than higher cognitive functions (e.g., language). Hence, examining the variability of brain lateralisation phenotypes across species may provide insights into the evolution of hemispheric asymmetries.

To conclude, we strongly agree with Guy Vingerhoets' perspective and challenges [15]. We believe that actions are needed to take the next critical steps towards multidimensional participant-centric analyses. Taking other successful initiatives [35] as an example, the initial step would be for researchers who investigate functional brain lateralisation to unite and pool efforts to create an extensive high-dimensional comprehensive database to harvest together as a consortium. This effort ensures a large database and productive collaborations within an open science framework to take the next steps together.

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