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METHODS PAPER

Categorical laterality indices in fMRI: a parallel with classic similarity indices

Mohamed L. Seghier[1]

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Abstract
FMRI-based laterality index (LI) is widely used to assess relative left–right differences in brain function. Here we investigated objective ways to generate categorical LI. By defining left and right hemisphere contributions as discrete random variables, it was possible to depict the probability mass function of LI. Its distribution has a shape of a symmetrical truncated exponential function. We demonstrate that LI = ± 0.2 is an objective cut-off to categorize classification of hemispheric dominance. We then searched for parallels between LI and classic similarity or association indices. A parallel between LI and Sorensen–Dice index can be established under maximal voxel-wise overlap between left and right hemispheres. To redefine LI as a proper distance metric, we suggest instead to relate LI to Jaccard–Tanimoto similarity index. Accordingly, a new LI formula can be derived: LI_{new} = LH–RH/max(LH,RH). Using this new formula, all LI_{new} values follow a uniform-like distribution, and optimal categorization of hemispheric dominance can be achieved at cut-off LI_{new} = ± 1/3. Overall, this study investigated some statistical properties of LI and revealed interesting parallels with classic similarity indices in taxonomy. The theoretical distribution of LI should be taken into account when quantifying any existing bias in empirical distributions of lateralization in healthy or clinical populations.

Keywords Lateralisation · Hemispheric dominance · Laterality index · Dice index · Jaccard index · Categorization cut-off · Probability mass function

Introduction

FMRI-based laterality index (LI) is widely used for assessing hemispheric dominance in a non-invasive way (Desmond et al. 1995; Binder et al. 1996), originally called the laterality quotient (Binder et al. 1995). It summarizes the relative normalized difference (distance) between the contribution of left (LH) and right (RH) hemispheres; see the following classic equation:

$$\mathrm{LI} = \frac{\mathrm{LH} - \mathrm{RH}}{\mathrm{LH} + \mathrm{RH}}, \quad (1)$$

LI varies from − 1 for pure RH dominance to + 1 for pure LH dominance (for the whole hemisphere or within a predefined region of interest (ROI), and assuming positive quantities: LH ≥ 0; RH ≥ 0; LH + RH > 0). This formula (Binder et al. 1995) was initially derived from Oldfield's laterality quotient of handedness (Oldfield 1971). Although this popular definition of LI is simple to compute, different methodological issues may complicate its interpretation; for a review, see Bradshaw et al. (2017) and Seghier (2008). There are many ways to quantify LI, depending on how the contributions of LH and RH are assessed. In early work for instance, Binder et al. (1996) used signal extent (suprathreshold voxel count) to assess LH and RH contributions, and Desmond et al. (1995) used the sum of the functional activation magnitudes in LH and RH. Since then, many alternative approaches have been introduced in the literature to boost the robustness of LI by minimizing its dependency to statistical outliers and by accounting for its variability with statistical thresholds. These alternative methods typically manipulate aggregate statistical scores (sum of correlations or *t* scores), signal change, distribution of voxels' statistics, adaptive thresholding, threshold-dependent curves, bootstrapping, and threshold-free measures; for a detailed review, see Seghier (2008) and Bradshaw et al. (2017). After

✉ Mohamed L. Seghier
mseghier@gmail.com

[1] Cognitive Neuroimaging Unit, Emirates College for Advanced Education, PO Box: 126662, Abu Dhabi, United Arab Emirates

quantifying LI, the next step is usually to categorize LI values into different dominance classes. Here, we address this important methodological issue regarding the definition of categorical LI values using objective cut-offs.

Categorical LI values are useful, for instance, when comparing fMRI-based LI values to standard clinical measures of hemispheric dominance such as Wada test (Janecek et al. 2013; Bauer et al. 2014). One common procedure is to apply a predefined (arbitrary) cut-off T to categorize LI values into three dominance classes, as following:

- Left hemispheric dominance if $LI > T$;
- Right hemispheric dominance if $LI < -T$;
- Bilateral representation if $|LI| \leq T$.

The arbitrary value of T varied between 0.1 and 0.5 in previous studies [see Seghier (2008) and Bradshaw et al. (2017) for more details]. Alternative schemes used a much refined categorization in five classes:

- Strong left lateralization if $LI > T_2$;
- Weak left lateralization if $T_1 < LI < T_2$;
- Bilateral representation if $|LI| \leq T_1$;
- Weak right lateralization if $-T_2 < LI < -T_1$;
- Strong right lateralization if $LI < -T_2$.

With T_1 and T_2 are two arbitrary cut-offs with $T_2 > T_1$. This scheme is, however, not widely used and was introduced mainly to explain some discrepancies between fMRI-based LI and clinical tests.

The exact number of useful dominance categories may depend on the specific brain function under study (e.g. language, spatial attention), the population of interest (e.g. healthy versus clinical populations with different brain disorders), and subjects' demographics (age, gender and handedness). One possible approach is to use data-driven methods on fMRI-based LIs to estimate the most useful number of dominance categories for a given population [e.g. Abbott et al. (2010) and Mazoyer et al. (2014)]. Although these empirical investigations provided interesting insights into typical/atypical lateralization, accurate estimation of the size of any existing bias in hemispheric dominance in normal or clinical populations requires a better understanding of the behaviour of LI when dealing with random variables.

Here we generated the distribution of LI for random events, and estimated objective cut-offs based on that theoretical LI distribution. We started by defining an exhaustive list of all possible LI values when using signal extent in left and right ROIs. By exploring the distribution of all LI values, objective cut-offs were then determined to demarcate the dominance categories. We also framed this question of categorical dominance classification within the field of taxonomy that is interested in the description and classification of organisms. Specifically, we described how to link LI to classic similarity or association indices (Cheetham and Hazel 1969; Hubalek 1982), which could potentially open a new avenue of knowing more about LI's behaviour.

LI distribution

We illustrated our rationale here with LI values based on binary quantities; for instance, LH and RH in Eq. (1) as discrete random variables corresponding to the number of suprathreshold voxels in left and right ROI, respectively. By construction, LI is agnostic to how voxels are spatially distributed within each ROI, because it is only sensitive to differences in size and not location, similar to the behaviour of volumetric distance measures; for more details, see Taha and Hanbury (2015). It is thus possible to generate an exhaustive set of all possible LI values and plot their distribution.

We set the total size of each ROI to N, which means LH or RH can take any discrete values from the set $\{0,1,2,\ldots N-1,N\}$. Our discrete sample space can be defined by listing all possible LI values (i.e. outcomes) that can be generated after combining a given number in the left ROI with a given number in the right ROI. This can be written as the set of all possible pairs (LH and RH). The cardinal of this set is $N^2 + 2N$. Applying Eq. (1) on all generated pairs yielded specific discrete LI values within the interval $[-1, 1]$.

Accordingly, all possible LI values are listable (countable). The smallest positive LI value is

$$\frac{1}{2N-1}. \tag{2}$$

The largest positive LI value (excluding $+1$) is

$$\frac{N-1}{N+1}. \tag{3}$$

For a given N, the range or sample space of all possible LI values is the exhaustive set denoted $\Omega = \{-1, (1-N)/(N+1), \ldots -1/(2N-1), 0, 1/(2N-1), \ldots, (N-1)/(N+1), +1\}$. The occurrence (frequency) of each discrete LI value can then be calculated.

Figure 1 illustrates the relative frequency of each possible value (i.e. occurrence of each element of set Ω). This can be defined as the probability mass function of LI. The shape of the probability mass function is valid for any N value, but by construction, the range (i.e. exact LI values) will depend on N. The plot in Fig. 1 shows that LI values (as outcomes) are not equally likely. The modes of LI are the integers $\{-1, 0, 1\}$ with a relative frequency of $1/(N+2)$. With fewer bins, the histogram of all possible LI values shows a symmetrical truncated exponential distribution. Around 50% of all possible LI values are within the interval $[-1/3, 1/3]$.

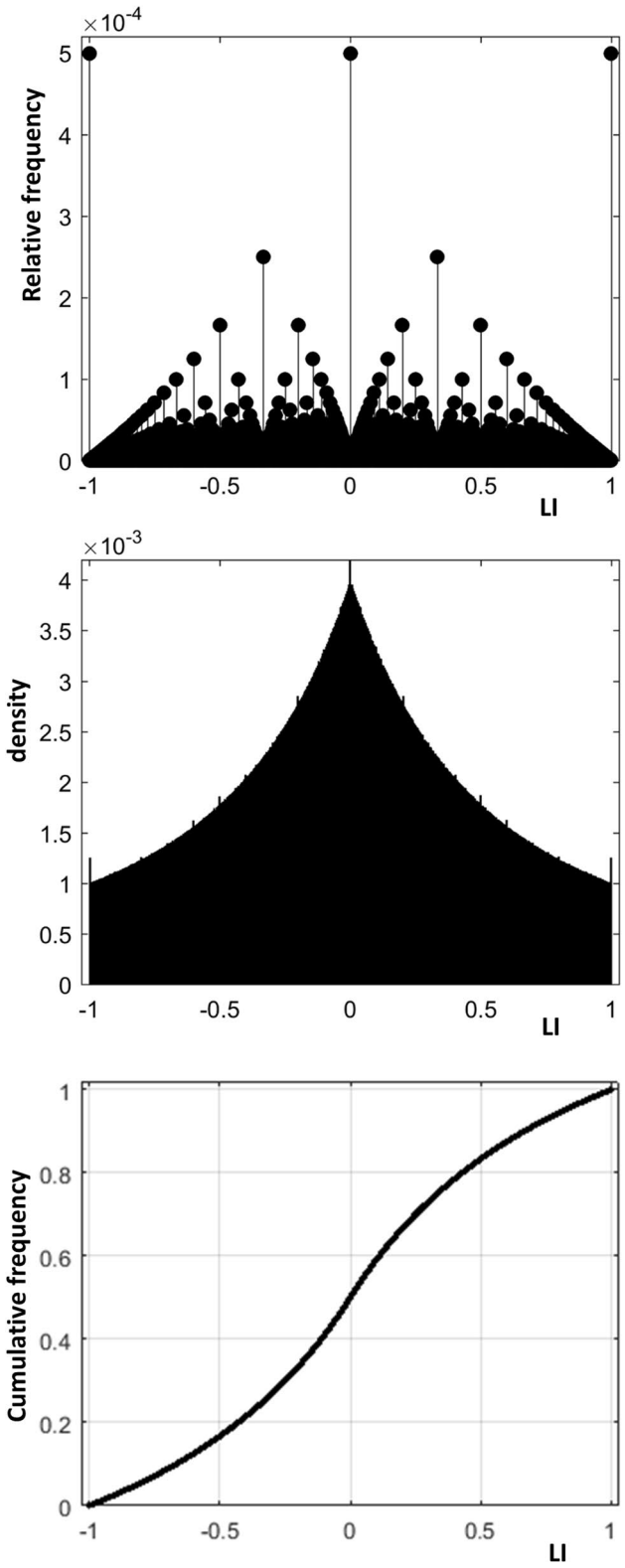

Fig. 1 Top: the relative frequency of each possible LI value for an arbitrary $N=2000$ voxels (i.e. occurrence of each LI value divided by all outcomes). Some LI values, by construction, are more frequent than other values (i.e. outcomes are not equally likely). This multimodal probability mass function has three modes $\{-1, 0, 1\}$. The most frequent value beyond the modes is $\pm 1/3$, corresponding to all possibilities where the contribution of one hemisphere is twice the contribution of the other hemisphere (i.e. LH = 2 * RH). Middle: the histogram of all LI values (calculated here with 500 bins). The histogram is representative for any N value, but smaller N values yield coarser histograms. The symmetrical histogram has a shape of a truncated exponential function. The three areas of the histogram between intervals $[-1, -0.2]$, $[-0.2, 0.2]$ and $[0.2, 1]$ are all equal to 1/3. Bottom: the cumulative distribution function of LI

We then searched for the optimal cut-off T that ensures the same likelihood for any randomly selected LI to belong to one of the three traditional dominance categories (left dominance, bilateral, right dominance). In other words, optimal cut-off T should satisfy the following equality between probabilities:

$$p(\mathrm{LI} < -T) = p(\mathrm{LI} > T) = p(\mathrm{LI} \geqslant -T, \mathrm{LI} \leqslant T) = \frac{1}{3}.$$

From Fig. 1, the only possible T value that satisfies this equality is $T=0.2$. This means that a randomly selected LI value has the same likelihood (33.33%) of falling in one of the following intervals $[-1, -0.2[$, $[-0.2, 0.2]$ and $]0.2, 1]$. In set theory, the cut-off $T=0.2$ guarantees sameness of cardinality (equipotent subsets), meaning the three categorical classes (as events) would have equal cardinals. Interestingly, this calculated T value corroborates with the current practice in the LI literature where the most frequent cut-off used in previous fMRI studies is 0.2 [see review in Seghier (2008) and Bradshaw et al. 2017)]. If more dominance categories are needed, for instance, to refine the definition of bilaterality [for a similar rationale in other contexts see (Fagard et al. (2015)], the same procedure can be used. For example, in case of five dominance categories, the following two cut-offs are recommended: $T_1=0.11$ and $T_2=0.43$ (T_1 and T_2 defined above).

LI and classic dissimilarity indices

In this section, we explored some parallels between LI and some classic indices used in taxonomy. Below, we considered LI as a measure of dissimilarity (distance) between quantities LH and RH, defined here as binary data or *taxa*. To illustrate our rationale, it was sufficient to only consider positive LI values given the symmetrical shape of LI distribution (cf. Fig. 1). We started by rearranging suprathreshold voxels in a homologous way between left and right ROI, so that each selected voxel in the right has a homologue in the left. Because the total number of voxels is unchanged within each region, this rearrangement does not impact on LI but it allows voxel-by-voxel comparison to be estimated, as in classic taxonomy studies. Fundamentally, this spatial rearrangement of voxels within each region maximizes the voxel-wise overlap between left and right ROIs.

We can now write the numerator and denominator of LI using logical operators 'OR' and 'AND' as follows:

$$\mathrm{LH} - \mathrm{RH} = \mathrm{OR}(\mathrm{LH}, \mathrm{RH}) - \mathrm{AND}(\mathrm{LH}, \mathrm{RH}), \tag{4}$$

$$\mathrm{LH} + \mathrm{RH} = \mathrm{OR}(\mathrm{LH}, \mathrm{RH}) + \mathrm{AND}(\mathrm{LH}, \mathrm{RH}), \tag{5}$$

where OR(LH, RH) is the union between left and right ROI and AND(LH, RH) is the intersection between the two regions. Because voxels are rearranged in a homologous way, the logical operators become:

$$\mathrm{OR}(\mathrm{LH}, \mathrm{RH}) = \max(\mathrm{LH}, \mathrm{RH}), \tag{6}$$

$$\mathrm{AND}(\mathrm{LH}, \mathrm{RH}) = \min(\mathrm{LH}, \mathrm{RH}). \tag{7}$$

Using a classic definition of Sorensen–Dice (SD) index:

$$\mathrm{SD} = \frac{2\mathrm{AND}}{\mathrm{OR} + \mathrm{AND}}. \tag{8}$$

By replacing AND and OR of Eq. (8) by the abovementioned definitions in Eqs. (4, 5, 6 and 7), we obtain the following relationship:

$$\mathrm{LI} = 1 - \mathrm{SD}. \tag{9}$$

This remarkably simple equation demonstrates that LI can be related to classic similarity indices, under maximal voxelwise overlap after spatial rearrangement. This opens an opportunity to know more about the behaviour of LI using the rich existing literature about classic indices in taxonomy.

Sorensen–Dice index has been shown to be a special case of the kappa statistic commonly used in reliability analysis (Zijdenbos and Dawant 1994). Although thresholds of around 0.7 were suggested (Zijdenbos and Dawant 1994; Zou et al. 2004), strong agreement or similarity between two quantities is commonly considered for values > 0.8 (McHugh 2012). Accordingly, using Eq. (9), LI less than 0.2 ($= 1 - 0.8$) means highly similar LH and RH (i.e. a bilateral representation), which is in line with the cut-off $T = 0.2$ obtained above from the distribution of LI. This link with the Sorensen–Dice index offers the possibility to use some previous probabilistic derivations to assess statistical significance of comparisons between laterality values [e.g. Johnston (1976), Snijders et al. (1990), Chao et al. (2006) and Albatineh (2010)].

New LI formula

As mentioned above, this link between LI and Sorensen–Dice index [Eq. (9)], after voxel rearrangement, provides an additional insight into the behaviour of LI (Wolda 1981; Snijders et al. 1990; Holliday et al. 2002; Warrens 2008). One important observation from previous studies is that Eq. (9) is not a proper distance metric because it does not possess the property of triangle inequality. However, it is possible to redefine LI in a way that would convert LI to a proper distance. Here we used a distance based on the Jaccard–Tanimoto index[1], because this index is a proper metric (Gower and Legendre 1986; Lipkus 1999; Kosub 2019). Accordingly, we can replace Sorensen–Dice index by Jaccard–Tanimoto index in Eq. (9), without altering the behaviour of LI given that Sorensen–Dice index is a monotone function of the Jaccard–Tanimoto index (Hubalek 1982; Paradowski 2015). Interestingly, because Jaccard–Tanimoto index is numerically more sensitive to mismatch when there is reasonably strong overlap, it would make sense to use it to magnify dissimilarities in the context of left versus right hemisphere differences.

More specifically, similar to Eq. (9), one may define a new formula for LI using Jaccard–Tanimoto (JT) index as follows:

$$\mathrm{LI}_{\mathrm{new}} = 1 - \mathrm{JT}, \tag{10}$$

with Jaccard–Tanimoto index defined as

$$\mathrm{JT} = \frac{\mathrm{AND}}{\mathrm{OR}}. \tag{11}$$

Using Eqs. (4–7) for operators AND and OR, we can derive a new formula for LI as follows:

$$\mathrm{LI}_{\mathrm{new}} = \frac{\mathrm{LH} - \mathrm{RH}}{\max(\mathrm{LH}, \mathrm{RH})}. \tag{12}$$

Using the same procedure as above, we can list all possible $\mathrm{LI}_{\mathrm{new}}$ values for a given ROI size N. The probability mass function of $\mathrm{LI}_{\mathrm{new}}$ is illustrated in Fig. 2. Interestingly, with fewer bins, the histogram shows a uniform distribution. Using the same procedure as above for LI, the three dominance categories (left dominance, bilateral, right dominance) can objectively be defined by selecting a cut-off $T = 1/3$ on $\mathrm{LI}_{\mathrm{new}}$. For higher number of dominance categories, different cut-offs can be easily estimated given the uniform distribution of $\mathrm{LI}_{\mathrm{new}}$. More specifically, for any C dominance categories, cut-offs T_{i} are equal to $-1 + \frac{2i}{C}$, with i varying between 1 and $C - 1$.

Last but not least, the following nonlinear relationship converts LI values to $\mathrm{LI}_{\mathrm{new}}$:

$$\mathrm{LI}_{\mathrm{new}} = \frac{2 * \mathrm{LI}}{1 + |\mathrm{LI}|}. \tag{13}$$

[1] Tanimoto distance is not always a synonym for Jaccard distance. For binary data, Tanimoto index can be defined as the ratio of the intersecting set to the union set (as in Equation [11], see also Todeschini et al. 2012). In that case, Equation [10] is a proper distance metric (Lipkus 1999). This distance is also called Soergel's distance.

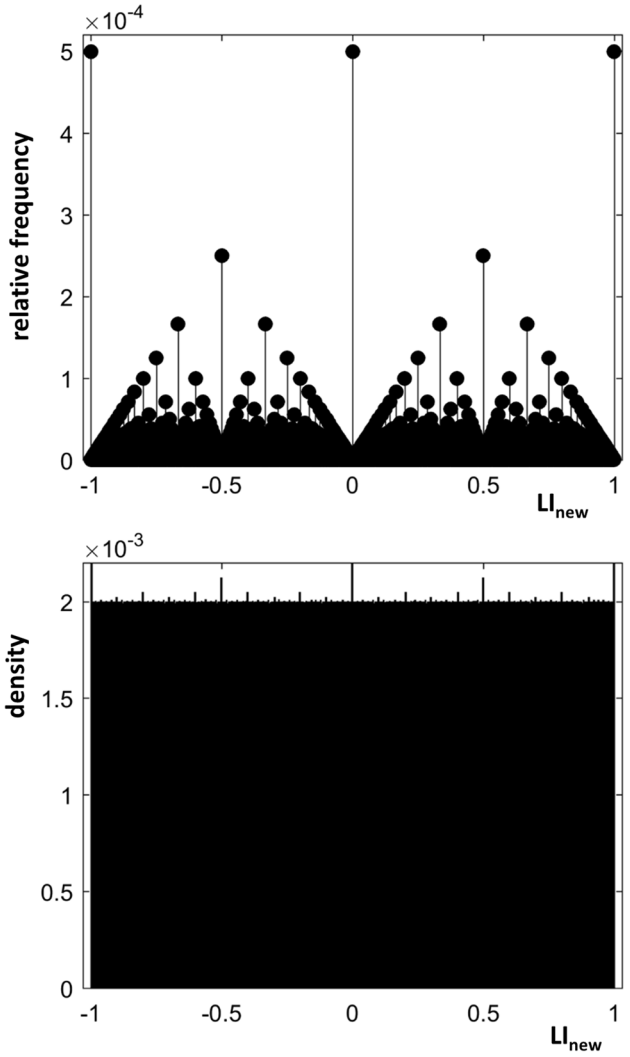

Fig. 2 Top: the relative frequency of each LI_{new} value. As the case for classic LI, some LI_{new} values are more frequent that other values (i.e. outcomes are not equally likely). The most frequent LI_{new} value beyond the three modes $\{-1,0,1\}$ is $\pm 1/2$, corresponding to all possibilities where the contribution of one hemisphere is twice the contribution of the other hemisphere (e.g. LH = 2 * RH). Bottom: the histogram of all LI_{new} values (calculated here with 500 bins) for $N = 2000$ voxels as in Fig. 1. The density of LI_{new} is uniform

Discussion

This study investigated the possibility to set objective cut-offs based on LI's probability mass function, so that categorical laterality indices can be defined. The definition of dominance categories was based here on some statistical properties of LI (cf. Fig. 1), with LH and RH defined as random discrete variables. The cut-offs T estimated here reflect the statistical nature of LI, and should not be equated with real dominance categories because the latter varies with task, ROI location, LI calculation scheme, and population demographics (Stroobant et al. 2009; Pinel and Dehaene 2010; Kong et al. 2018). More specifically, the theoretical distribution of LI does not necessarily match the observed distributions of lateralized brain functions in healthy and clinical populations [e.g. Knecht et al. (2000), Whitehouse and Bishop (2009), Drane et al. (2012), Cai et al. (2013) and Mazoyer et al. (2014)]. This is a consequence of the inherent bias in the distribution of brain lateralization in human populations due to many complex factors (Geschwind and Galaburda 1985; Bishop 2013; Corballis 2014; Kong et al. 2018), which implies that lateralization degrees for a given brain function occur with unequal probability in real contexts.

Perhaps more importantly, the definition of dominance categories will have a strong implication on the exact proportions of typical and atypical lateralization in a given group/population. We note that the cut-offs used to define dominance categories were inconsistent across previous fMRI studies (Bradshaw et al. 2017; Seghier 2008). They were typically set as arbitrary thresholds with no clear relevance to real bias in lateralisation for a given brain function. In the absence of prior knowledge, users can use by default our objective statistical definition of cut-offs. Fundamentally, irrespective of the exact physical meaning of a given cut-off, one needs to appreciate that LI is a reductionist mapping of a 3D fMRI activation pattern (with thousands of voxels) into one dimensionless laterality value that is intuitive and easy to interpret (Seghier et al. 2011). The particular way this mapping is encoded [Eq. (1)] has implications on the statistical properties of LI (e.g. compare LI versus LI_{new} distribution). This means that in the absence of prior knowledge about the size of real lateralization bias in a given population, it would make sense to use objective cut-off T when defining dominance categories so that no artificial bias is introduced by that mapping.

This issue is critical when studying the proportion of typical versus atypical lateralized individuals for brain functions that are expected to show widespread between-subject variability (i.e. when more than one dominance category may exist) (Whitehouse and Bishop 2009). For instance, in the language domain, for previous studies that used lower cut-offs (e.g. $T = 0.1$), the proportion of bilateral lateralizations might have been underestimated, whereas the proportion of strongly lateralized individuals might have been overestimated. Likewise, for previous studies that used higher cut-offs (e.g. $T = 0.5$), the proportion of bilateral lateralizations might have been overestimated, whereas the proportion of lateralized individuals might have been underestimated. The use of different cut-offs across studies may have exacerbated or cancelled out the real bias in laterality.

The analysis of LI's distribution and the definition of objective cut-offs were shown here for LH and RH as discrete variables (e.g. voxel count). Previous studies have defined arbitrary cut-off T values irrespective of the method

used to compute LI values, including methods based on signal extent, signal magnitude or the distribution of statistical scores. However, there is no straightforward way to convert one LI calculation method to another method, and previous work has shown that different methods may yield different empirical distributions of LI (e.g. Jansen et al. 2006; Chlebus et al. 2007). Future research needs to examine how our estimated objective cut-offs generalize to other LI calculation methods (i.e. when LH and RH are not discrete variables). For the specific case of methods that rely on linear combination (e.g. average) of LI values calculated on the basis of signal extent over different thresholds, the same cut-off of $T = 0.2$ can be used to define dominance categories. For other LI calculation schemes, if objective cut-offs cannot be determined theoretically, data-driven categorisation may offer a way to conquer this problem (Mazoyer et al. 2014). Alternatively, as discussed below, Eqs. (9) and (10) might hold the key to tackle this issue given that many classic similarity indices have definitions that extend to continuous variables.

The link suggested here between LI and classic similarity indices opens a new opportunity to examine the properties of LI through the lenses of the rich taxonomy literature (Choi et al. 2010; Todeschini et al. 2012). One important issue is to appreciate the probabilistic basis of LI using previous studies that investigated theoretical distributions of similarity indices (Snijders et al. 1990; McCormick et al. 1992; Real and Vargas 1996; Real 1999). In addition, it is possible to adjust LI in a context-specific manner to boost its robustness for a given data type (Ivchenko et al. 1995; Fligner et al. 2002). For instance, previous studies have shown the possibility to adjust classic similarity indices for different non-binary data such as probabilities (Cha 2007) and other continuous variables (Barbosa 2015; Hwang et al. 2018). This offers optimal ways to combine a variety of fMRI measures in LI computation [as reviewed in (Seghier 2008; Bradshaw et al. 2017)], while optimizing it with respect to many other methodological issues, see examples in Albatineh et al. (2017).

In summary, when using classic LI formula [e.g. Eq. (1)], a cut-off of ± 0.2 is recommended in case of three useful dominance categories, providing that binary LH and RH quantities are based on signal extent. It is important to mention that any definition of an objective cut-off would depend on how LI values were computed in the first place, including, for instance, as a function of the number of suprathreshold voxels, signal magnitude, statistical scores, or their distributions in case of threshold-free LI values. The new LI definition [cf. Equation (12)] ensures that LI is a proper distance metric. Using this new formula, LI values can be classified into three dominance categories at cut-offs $\pm 1/3$, to yield an equal random cumulative probability in each dominance category. In the absence of clear hypotheses or prior knowledge of the size of real lateralization bias in healthy or clinical populations, future studies can use the estimated objective cut-off T to generate categorical laterality indices. This will improve consistency between studies so that the proportions of typically and atypically lateralised individuals can be compared across studies.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Ethical approval For this study with synthetic/simulated data only, formal consent is not required.

Research involving human participants This article does not contain any data from human participants or animals.

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