The validity and reliability of quantifying hemispheric specialisation using fMRI: Evidence from left and right handers on three different cerebral asymmetries

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ABSTRACT

Neuroimaging has tremendous potential for quantifying hemispheric specializations. However, the possibilities remain under-utilized, in part, given some of the complexities in quantifying any differences in a reliable, transparent fashion. A second issue with hemispheric asymmetries is that they are extremely one-sided in most people. This skew limits the generalisability of any findings to those participants with rarer forms of cerebral asymmetry. Here, we demonstrate usefulness of an approach developed by Wilke and Lidzba, (J Neurosci Meth, 163, 2007), which allows for threshold-independent estimates of cerebral asymmetry to be calculated in individual participants. We compared these estimates from two separate runs for three different cerebral asymmetries in the same participants. We circumvented the skewed nature of this type of data in two ways; first, we scanned a large number of non-right handed participants, and second, we included asymmetries that favour the right hemisphere in right handers, which we had reason to believe were less skewed than those related to speech and language. Verbal fluency and two visuoperceptual asymmetries were localized in a sample of 33 right handed and 60 non-right handed participants. Laterality indices (LIs), which quantify the direction and strength of an asymmetry, were calculated for BOLD activity relating to language, face perception, and body perception in each run separately. Run 1 - run 2 correlations were all statistically significant and surprisingly sizeable ($r = 0.89$ to $r = 0.62$), considering the relatively short amount of time on task within our particular localizers. This noteworthy success validates a number of useful ways that functional neuroimaging can be used to advance understanding of cerebral asymmetries.

Cerebral dominance, in our species at least, was a central research theme in behavioural neurology and neuropsychology for much of the 20th century. Paradoxically, given the tremendous possibilities afforded by the development of structural and functional imaging techniques, most cognitive neuroscientists in language and attention, for example, have avoided detailed exploration of differences across the median longitudinal fissure. Instead, they focus on localizing regions and networks within hemisphere. In their publications, asymmetries in threshold-dependent averaged activation maps of the whole group are mentioned, often in passing. They are briefly related to previous neuropsychological literature, confirming that the function in question is indeed localized to the same hemisphere by neuroimaging as was found in the relevant older, neuropsychological literature.

In fact, fMRI with neurologically-intact individuals has several advantages for cerebral asymmetry research. First, making inferences about functions based on lesions in brain-damaged participants can be problematic; Richard Gregory famously likened that process to working out how a radio works by removing individual pieces (Gregory, 1961). Second, given the "head start" provided by concentrated and continuous research since the 1990s (e.g. Corbetta et al., 1990; Kanwisher et al., 1997; McCarthy et al., 1997; Petersen et al., 1988), considerable headway has been made regarding the neural substrates of attention, visual perception, and language. Such advances are exploitable for informing best practice in block and event-related fMRI design, analysis and interpretation in studies of hemispheric specialization. Third, the recent push for making neuroimaging data publicly available means that large datasets using similar cerebral asymmetry "localizers" can be compared with one another and in some circumstances aggregated (albeit with

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caution).

A major limitation of measuring cerebral asymmetry is that, for functions such as speech and language, at the very least, the data is particularly skewed. For example, most people are left lateralized for speech/language functions, however these are assessed (Bryden, 1982; Carey and Johnstone, 2014; Gazzaniga and Hillyard, 1971; Rasmussen and Milner, 1977). To add to this state of affairs, handedness, relevant in a rather complex way to the rarer kinds of cerebral asymmetry (Baynes and Long, 2007; Elias et al., 1998; Gerrits et al., 2019; Joliot et al., 2016; Levy et al., 1983; Ocklenburg et al., 2014; Willems et al., 2014) is also skewed. Most people are right handed (about 90%), and the vast majority of them have left hemispheric dominance for speech and language. Right hemispheric dominance for these functions is somewhat more common in non-right handers, but is still relatively rare (Badzakova-Trajkov et al., 2010; Carey and Johnstone, 2014; Knecht et al., 2000; Mazoyer et al., 2014; Rasmussen and Milner, 1977; Whitehouse and Bishop, 2009).

One consequence of the rarity of non-right handedness and the link (albeit not a strong one) to unusual language asymmetry is obvious. If a goal of a research project is to relate cerebral asymmetry to some other variable of interest, or, for example, to describe the range of possible combinations of multiple asymmetries, non-right handers need to be tested in relatively large numbers in order to find those rare individuals who are right hemisphere dominant for language (e.g. Badzakova-Trajkov et al., 2010; Badzakova-Trajkov et al., 2016; Cai and Van der Haegen, 2015; Goldenberg, 2013; Hunter and Brysbaert, 2008; Mazoyer et al., 2016; Van der Haegen and Brysbaert, 2018; Van der Haegen, Cai and Brysbaert, 2012; Vingerhoets, 2019a, 2019b; Vingerhoets et al., 2013; Willems et al., 2014). This requirement for active recruitment of non-right handers has been long recognized by scientists pursuing questions on handedness and/or hemispheric differences (Boles, 1996; Bryden, 1965). In stark contrast to that quite common approach in neuropsychology, neuroimagers tend to avoid non-right handers as a rule of thumb (for language and speech experiments, at least, Willems et al., 2014).

A second, less appreciated consequence of the subtle "asymmetrical" asymmetry between the majority right hander and the rarer non-right hander is that differences between these two groups can inform the likely relationship of a function to speech and language hemispheric specialization (Karlsson et al., 2019; Van der Haegen and Brysbaert, 2018). Furthermore, individuals with the rarer "atypical" asymmetries (which *may* be more common in left handers for asymmetries that are not speech and language-related) enable testing biological constraints on how that function must or can operate within and across hemispheres.

Setting the problem of skew to one side, quantifying cerebral asymmetries in groups, let alone in individual people, can be challenging. There have been a number of attempts to do so using neuro-imaging, for language-related functions at least (many in the epilepsy literature in part due to the attempts to circumvent sodium amytal testing presurgically, e.g. Berl et al., 2014; Binder et al., 1996; Janecek et al., 2013; Springer et al., 1999; Tailby et al., 2017; Woermann et al., 2003), but these have their limits. The most frequently used method used for the neuroimaging data in such studies quantifies the number of voxels (or clusters of voxels of some minimum number) in each hemisphere in a group-averaged t-map. Another approach has been to compare activation patterns in the two hemispheres by reversing the y-axis of the activated voxels in one of the two hemispheres. By over-laying one hemisphere on the other, statistics can compare hemispheres on the same contrast to determine if they differ significantly from one another or not. For example, Westerhausen et al. (2014) created a mirror-reversed beta weight mask which, when subtracted from the original, provided a measure of which voxel, left hemisphere or right, had the larger beta value.

There are two limitations with these types of approaches. First, if they depend in any way upon a group-defined statistical threshold,

dramatically different levels of BOLD signal in different individuals survive. Such selection results in differential contributions of different people to any group composite map or statistic (one solution to this problem could be to set a number of activated voxels for a contrast in individual participants; see Fesl et al., 2010 and Jansen et al., 2006, although justifying the precise number a priori would be a useful first step). Second, the specific threshold chosen by the researchers will provide a different measure of asymmetry for the group (and of course the individuals within it) than a slightly lower or slightly higher threshold used on the identical dataset (Abbott et al., 2010; Adcock et al., 2003; Liegeois et al., 2002; Seghier, 2008; Wilke and Lidzba, 2007; reviewed in Bradshaw et al., 2017a).

These limitations are now circumventable. Threshold-independent techniques have been proposed to assess cerebral asymmetries in fMRI data, the most popular of which to date (revealed in the review by Bradshaw et al., 2017a) is implemented in an SPM toolbox (Wilke and Lidzba, 2007; see also Wilke and Schmithorst, 2006). This LI toolbox allows for comparison of right and left hemispheres without the complications that arise from threshold-dependent methods. It is used on datasets from single participants, important for any attempts to quantify the "breadth" (i.e., how many) of typical and atypical asymmetries (Karlsson et al., 2019).

In the cerebral asymmetry literature, the LI toolbox has been used by groups who also attempted to reduce the skew of the sort mentioned above (although it is not usually described in this manner). Three research teams (Auckland: Badzakova-Trajkov et al., 2010; Häberling et al., 2016a, 2016b; Bordeaux: Mazoyer et al., 2016; Zago et al., 2016; and Ghent: Cai, Van der Haegen and Brysbaert, 2013; Van der Haegen, Cai, Seurinck and Brysbaert, 2011) have performed the majority of this work to date: recruiting, pre-screening and scanning large numbers of non-right handers.

These large studies with active pursuit of non-right handers have yet to examine the reliability of the laterality coefficients obtained for language, let alone non-language functions that tend to favour the non-linguistic hemisphere. A small number of earlier experiments have examined reliability in language tasks, but these tend to be rather more detailed analyses of a small number of right-handed participants (e.g. Chen and Small, 2007) and they have not examined lateralization indices per se (with the exception of a few small studies in right handers; Morrison et al., 2016; Rutten et al., 2002). Two exceptions from fMRI needs mentioning here: Harrington et al. (2006) using two different threshold-dependent techniques (one volume based and one based on the magnitude of the relevant statistical contrast) who found the best test-retest correlations with verb generation (fortuitously the task we had chosen for the study here) in ten healthy right handed people. Fesl et al. (2010) used a free reversed word association task on a larger sample that included non-right handers. They report a remarkably high test-retest correlation on a global network measure of asymmetry (Fesl et al., 2010).

Establishing the *validity* of specific neuroimaging methods for estimating of different cerebral asymmetries is more challenging. Although task-specific fMRI activations can be compared to previously published work in order to confirm similar localizations of functions, such data cannot speak to whether or not the estimated asymmetry is a valid and generalizable one. The exception to this limitation comes from the neuropsychology of language. In this domain, many well established techniques, including estimates of dominance frequency based on aphasia after unilateral lesions (e.g. Brain, 1945; Kimura, 1983; Zang-will, 1960; reviewed in Carey and Johnstone, 2014), provide a reasonable starting point for comparison with newer neuroimaging techniques. Furthermore, the well-established differences between right- and non-right handed people can be exploited.

As part of a larger, long-term project on measuring multiple behavioural, perceptual and cerebral asymmetries, we decided to interrogate some of the data from our first study on these questions. In the current investigation, we examined the reliability and validity of using

threshold-independent LIs with three well-described fMRI localizers. For assessing lateralization of language, we adopted a subvocal verbal fluency measure that has been validated against the Wada technique in epileptic patients (Abbott et al., 2010) and has been frequently used in the growing fMRI asymmetry literature (Biduła et al., 2017; Häberling et al., 2016a, 2016b; Hunter and Brysbaert, 2008; Powell et al., 2012). For faces and bodies, we took advantage of a locally-available visual perception localizer, where visual stimuli are processed in a one-back task (Downing et al., 2007; Peelen et al., 2006).

1. Methods

1.1. Participants

Ninety-three participants took part in this experiment, 33 right handed (21 female) and 60 non-right handed (22 female). All were members of the Bangor University community. Two participants (both non-right handed, one male and one female) were excluded from the analysis due to excessive head movement (>4 mm). The right handed participants- had a mean age of 26.09 (SD = 5.92) and a mean Waterloo handedness questionnaire (WHQ; Steenhuis and Bryden, 1989: −30 completely left, to +30 completely right) score of +28.00 (SD = 2.06). The non-right handed had a mean age of 24.83 (SD = 7.55), and a mean WHQ score of −20.38 (SD = 13.31).

1.2. Language localizer

A verbal fluency style paradigm was employed. Both an active and a control condition were used in a blocked design. Fourteen active and 14 control blocks were alternated with 30 rest blocks, each with a duration of 15 s. In the active blocks, participants were presented with a single letter in the middle of the screen for the duration of the block. During this time, participants were instructed to silently think of as many words as they could which began with that letter. A practice phase was run outside the scanner using the letter "D". In the control blocks participants were shown either the letter string "RARA" or "LALA", and were instructed to covertly repeat these non-words for as long as they were presented on the screen. In the 30 rest blocks a fixation cross was presented and participants were instructed to relax. The 14 letters chosen were the letters that begin the most words in English: T, A, S, H, W, I, O, B, M, F, C, L, D, P (as reported in the Natural Language Toolkit 3.0 - http://www.nltk.org). This task was presented across two runs, comprising seven active/control blocks per run. The letters were randomly presented in any order across these two runs.

1.3. Four condition face/body localizer

A face/body localizer was used to identify any asymmetry in face- and body-selective brain activation. The task involved viewing blocks of images from the categories: faces, bodies, chairs, and scenes. Whilst viewing the stimuli, participants completed a simple one-back task, pressing a button if they saw a consecutive, repeated image. Which hand participants held the button box in was counterbalanced within the right handed and non-right handed groups. Each localizer run consisted of 16 active blocks (4 for each stimulus category) and 5 rest blocks (taking place in block 1, 6, 11, 16 and 21). Each block lasted 16 s during which 16 images were displayed for 300 ms followed by a blank screen for 700 ms. Participants completed two runs of this task, with two different fixed stimulus orders, which were counterbalanced across participants, separately for the right handed and non-right handed groups.

1.4. fMRI acquisition

All scans were acquired in a Philips 3 T Achieva magnetic resonance scanner, using a 32-channel head coil, located at the Bangor Imaging Unit at Bangor University. Functional images were acquired with the following parameters: a T2-weighted gradient-echo EPI sequence; field of view (FOV) = 220 × 220, acquisition matrix = 96 × 96, 36 slices were acquired; acquired voxel size (mm) = 2.3 × 2.3 x 2.5 (reconstructed voxel size (mm) = 2.3 × 2.3 x 2.5). Verbal fluency (repetition time (TR) = 2500 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°) consisted of two runs of 174 volumes, and the face/body localizer (TR = 2000 ms, TE = 30 ms, FA = 90°) consisted of two runs of 166 volumes. The first 5 scans of each functional run were discarded before image acquisition to establish steady-state magnetization. High resolution T1-weighted structural images were obtained with the following parameters: T1-weighted image acquisition TR = 12 ms, TE = 3.5 ms, FA = 8°, FOV (mm) = 240 × 240, acquisition matrix = 80 × 79; 175 contiguous slices were acquired, voxel size (mm) = 1 × 1 x 2 (reconstructed voxel size = 1 mm^3).

1.5. Design and analysis

All MRI data were pre-processed and analyzed using SPM12 (Wellcome Department of Cognitive Neurology, University College London, http://www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB R2015b 8.6 (Mathworks Inc., Sherborn, MA, USA). Anatomical images were first manually aligned to the anterior and posterior commissure (AC-PC). Preprocessing of functional scans consisted of corrections for head motion (spatial realignment; trilinear interpolation), and images were realigned to the first functional volume of the first session (the volume closest to the anatomical scan). Functional scans were coregistered to their corresponding individual anatomical scans and normalized to standard MNI space (3 mm isotropic voxels). Normalized data were then spatially smoothed using a Gaussian kernel of 6 mm full-width at half-maximum.

The general linear model was used to map the hemodynamic response curve onto each experimental condition using boxcar regressors. This boxcar function was then fitted to the time series at each voxel resulting in a weighted beta-image. The fitted model was converted to a t-statistic image, comprising the statistical parametric map. To assess hemispheric contribution for processing a particular stimulus type, the LI-toolbox plugin for SPM was used (Wilke and Lidzba, 2007; Wilke and Schmithorst, 2006). This toolbox allows for comparison of right and left hemispheres without the commonly cited problems in doing so (such as complications that arise from statistical outliers, threshold-dependent comparisons, data sparsity and not taking regional variability of activation into account; Wilke and Lidzba, 2007). The result is a more standardized evaluation of laterality effects. This toolbox also provides an estimate of *how* lateralized a participant is for a given contrast (what we refer to elsewhere as the depth of asymmetry for an individual or a group; Karlsson et al., 2019). In this report, we calculate separate estimates of the LI from two separate runs of the localizer in question, in order to evaluate the likelihood that these asymmetries are relatively stable.

The toolbox employs a bootstrapping method whereby 20 equally-sized thresholds are calculated between 0 and the maximum t-value in the dataset. At each threshold, 100 bootstrapped samples (with a resampling ratio of k = 0.25) are taken at each threshold in each hemisphere. The 10,000 LI combinations are calculated from these samples for all surviving voxels on the left and right, with the standard LI formula (LI = (R - L)/(R + L)), where a resulting positive score indicates more left hemisphere activity, and negative indicates more right. To avoid effects due to statistical outliers only the central 50% of data are kept. A final LI is calculated from all the LIs weighted to their corresponding threshold.

We calculated whole brain LIs for each task for the following contrasts: fluency > letter strings, faces > scenes, and bodies > chairs. The latter two are regularly used in the face and body literature (Downing et al., 2007; Taylor et al., 2007). Whole brain analyses were carried out for each contrast, except for fluency > letter string where the cerebellum was excluded, as cerebellar involvement in language processing is

contralateral to the activation of the cerebral cortex (e.g. Gelinas et al., 2014; Häberling and Corballis, 2016; Jansen et al., 2005). Whole brain LIs were calculated to avoid any circularity of choosing regional ROIs known to be asymmetrical (LIs calculated in these two ways are highly correlated with one another, but unsurprisingly slightly stronger in the regional approach, see supplementary materials for data on fluency using a frontal lobe ROI versus the whole brain LIs reported below). To analyze the relative reliability of these three LIs, in terms of both strength and direction, Pearson's correlations were used. Additionally, the proportion of the samples showing a directional change across the two runs was recorded. Finally, the proportions of right handed and non-right handed participants who show the typical (i.e. majority) and atypical pattern of hemispheric dominance were reported. These data, for language at least, can provide evidence for the validity of the particular localizer, as proportions of typical and atypical dominance are quite well established.

2. Results

2.1. Language localizer

For purposes of estimating the validity of this task, we calculated the proportions of right handed and non-right-handed participants who have LIs of >0 on this task. The right handers were all left lateralised with the exception of two participants (32/34 = 94%). The majority of non-right handers were also left dominant (42/57 = 74%). Three correlations were run on the following comparisons: run 1 versus run 2 for all participants and all contrasts, separately for each handedness group. Finally, we used the average LI across both runs to classify individuals as showing typical dominance (i.e. the majority category) and atypical (the minority) dominance.

Of the 91 participants in this sample, only two participants, both non-right handers, changed the direction of their asymmetry from run 1 to run 2 (see Fig. 1). A significant correlation was found when comparing the LIs from run 1 with those from run 2 ($r = 0.92$, $p < .001$, $r^2 = 0.85$; 95% CI 0.88, 0.95). LIs across runs were compared for right handed and non-right handed samples separately, resulting in equivalently strong correlations for both groups ($r = 0.84$, $p < .001$, 95% CI = 0.70, 0.92, and $r = 0.92$, $p < .001$, 95% CI = 0.87, 0.95 respectively). Finally, correlations were also calculated separately for those with typical (n = 74) and atypical (n = 17) language dominance (as measured by an LI calculation from both runs of data), resulting in a significant correlation for both samples (typicals: $r = 0.60$, $p < .001$, 95% CI = 0.43, 0.73; atypicals: $r = 0.77$, $p < .001$; 95% CI = 0.46, 0.91).

Of the 17 participants with atypical language dominance (as measured by an LI calculation from both runs of data), all participants had consistent, rightward asymmetry, in both separate runs. Of those with typical dominance (both runs), only the two non-right-handers mentioned above reversed their asymmetries across runs.

2.2. Face localizer

Six right handed and 11 non-right handed participants changed the direction of their asymmetry across the two runs of this task (see Fig. 2). Of these individuals, 9 (5 non-right-handers) had atypical left hemispheric face dominance as measured from the average of both runs. A significant correlation was found when comparing the LIs from run 1 with those from run 2 ($r = 0.72$, $p < .001$, $r^2 = 0.52$, 95% CI = 0.60, 0.81). LIs across runs were compared for right handed and non-right handed samples separately, resulting in strong correlations for both groups ($r = 0.59$, $p < .001$, 95% CI = 0.31, 0.78; and $r = 0.76$, $p < .001$, 95% CI = 0.63, 0.85, respectively). Finally, correlations were also calculated separately for those with typical right hemisphere (n = 59) and atypical left hemisphere (n = 32) face dominance (as measured by an LI calculation from both runs of data), resulting in a significant correlation for those with typical face dominance ($r = 0.35$, $p = .006$, 95%
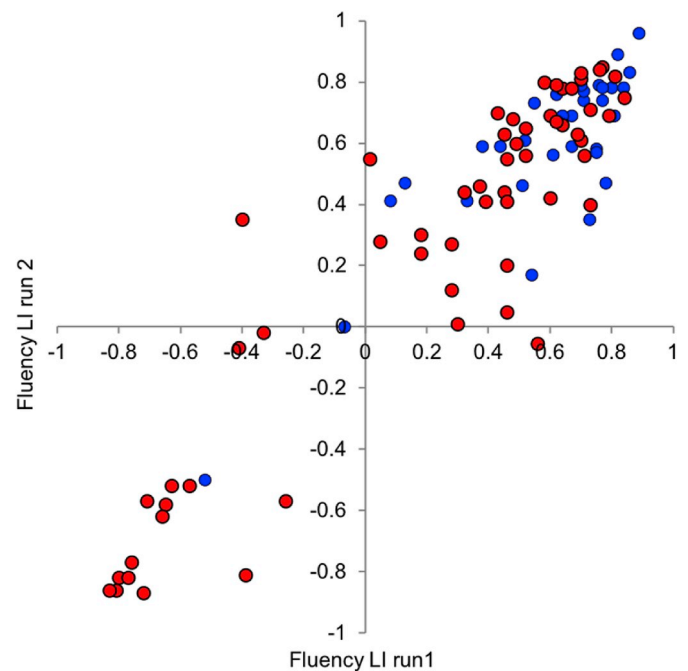
Fig. 1. Scatterplot of the LI scores across the two runs of the verbal fluency language task. In this and subsequent figures, blue datapoints indicate right-handed participants, and red datapoints represent non-right handed participants. Positive LIs indicate more activation in the left hemisphere. Typical dominance refers to the majority bias, which in this instance is presented by the upper (run 1, x axis) and right (run 2, y axis) halves. Therefore, consistently typical individuals appear in the upper right quadrant (left hemispheric on both run 1 and run 2). Participants falling into the bottom-left and upper-right quadrants did not change direction in their asymmetry across the two runs. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
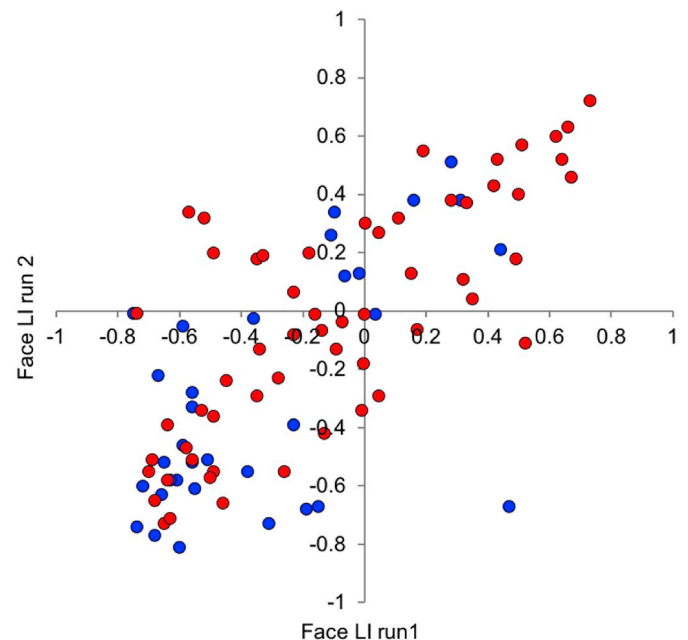
Fig. 2. Scatterplot of the LI scores across the two runs of the face localizer task. It is likely that the increased number of participants in the upper-left and bottom-right quadrants as compared with the language localizer data is due to the decrease in power obtained across these runs.

CI = 0.10, 0.56) and those with atypical face dominance (r = 0.42, p = .016, 95% CI = 0.08, 0.67).

2.3. Body localizer

Twenty participants, 6 right handed and 14 non-right handed, changed the direction of their asymmetry across the two runs of this task (see Fig. 3). Of these individuals, 8 (7 non-right handers) had atypical left hemispheric body dominance as measured by the average of both runs. A significant correlation was found when comparing the LIs from run 1 with those from run 2 (r = 0.62, p < .001, r^2 = 0.38; 95% CI = 0.48, 0.73). LIs across runs were also compared for right handed and non-right handed samples separately, resulting in a significant correlation for non-right handers (r = 0.63, p < .001, 95% CI = 0.45, 0.76), but not right handed participants (r = 0.29, p = .093, 95% CI = −0.06, 0.58). Finally, correlations were also calculated separately for those with typical right hemisphere (n = 69) and atypical left hemisphere (n = 22) dominance for body perception (as measured by an LI calculation from both runs of data), resulting in a significant correlation for those with typical dominance (r = 0.26, p = .028, r^2 = 0.07, 95% CI = 0.03, 0.47) but not those with atypical dominance (r = 0.31, p = .163, 95% CI = −0.13, 0.65).

3. Discussion

This investigation was designed to assess the validity and reliability of using fMRI to quantify threshold-independent cerebral asymmetries in individual people. We used the laterality toolbox (Wilke and Lidzba, 2007; Wilke and Schmithorst, 2006) to do so, increasingly the tool of choice for asymmetry researchers. Compared to previous related attempts which examine fMRI measurement reliability in individuals, our approach capitalises on the established neuropsychology of asymmetry. We actively recruited non-right handed individuals, a population likely to include some people with atypical cerebral dominance for language at least. Furthermore, we included two asymmetries thought to favour the right hemisphere (in right handers at least), which we suspected might be less skewed than fluency (Karlsson et al., 2019).
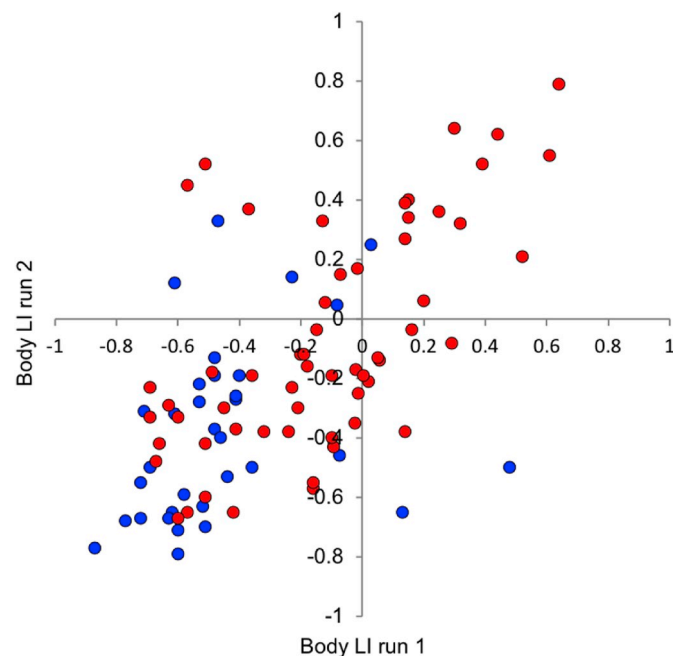

Fig. 3. A scatterplot of the LI scores across the two runs of the body localizer task.

3.1. Validity

In our meta-analysis of language dominance (Carey and Johnstone, 2014), we have shown that estimates from several non-imaging techniques all point to a 15–20% reduction in left hemispheric bias in non-right handed samples (Carey and Johnstone, 2014). Our data here largely reflect this difference, with left lateralization present in 94% of the right handers, and 74% of the non-right handers. These numbers are remarkably similar to the usual estimates for these two groups reported in Wada testing (e.g. Rasmussen and Milner, 1977). Our obtained proportions of left dominance in both the right- and the non-right handers in the present study provides some evidence of the validity of the use of the LI toolbox with subvocal verbal fluency data.

This conclusion is made with caution however. Although validity is often measured via concordance of results from two different methods, we propose that the use of a two-method approach should be complemented by the sizable literature on the expected proportions of typical and atypical lateralization for language as a function of handedness group. Having said that, functional transcranial Doppler sonography (fTCD) and/or Wada data from the same individuals studied with fMRI could certainly have helped to confirm how well our methods provide accurate classification (e.g. Janecek et al., 2013; Stroobant and Vingerhoets, 2000; Wegrzyn et al., 2019). Unfortunately, there are some limitations in the literature on congruence of fMRI versus Wada estimates of language dominance. Many of these techniques in early days had rather small samples (Desmond et al., 1995), and selection criteria for the patients are relatively sparsely described. A few attempts have used multiple speech arrest measures which in theory can produce a Wada-derived LI which could be compared to an fMRI-derived LI. Unfortunately, this multiple Wada measure approach has not been standardized or psychometrically assessed (Knecht et al., 2000). fTCD has been used for some years now to quantify magnitude of asymmetry (Stroobant and Vingerhoets, 2000) and several papers have cross validated this technique with estimates from fMRI (Deppe et al., 2000; Somers et al., 2011; Chilosi et al., 2014). The earliest papers of this sort, much like early fMRI work, made much of the agreement of a newer technique with an older, more established one. In fact, in rare circumstances where the estimates do not agree, there is little evidence to judge which estimate is the more valid of the two.

Of course, for the typical and atypical estimates from the Wada test, speech arrest (or equivalent) is used to dichotomously categorise cerebral dominance. Some theorists argue that only processes that are quite "late" in language and speech networks are truly lateralized. For example, in the popular neurobiological model of language advanced by Hickok, Poeppel and colleagues, only processes which they describe as "articulatory" and/or sensorimotor are largely left hemispheric (Hickok and Poeppel, 2007; Guenther and Hickok, 2016). The proportional approach advocated here could also be used to interrogate models that claim more or less lateralization for different components of the language system architecture (see Seghier et al., 2004, for an early example, and more recently Piervincenzi et al., 2016; and Woodhead et al., 2018).

Unlike this considerable literature on methods to quantify language dominance, it is less clear what to compare our two "right hemispheric" asymmetries with, to provide evidence for their validity from a hemispheric specialization perspective. The group-average threshold-dependent maps (which as always imply asymmetry, but should not be used to estimate their magnitude) at least suggest considerable overlap with many published reports of specialized regions in the occipito-temporal cortex that are relatively selective for face stimuli (Duchaine and Yovel, 2015; Gobbini and Haxby, 2007; Kanwisher, 2010). We did, while collecting these data, communicate with Prof Galit Yovel (https://people.socsci.tau.ac.il/mu/galityovel/), who kindly provided us with left and right fusiform face area volumes for 50 right handed participants assessed in her laboratory. Although her estimates depend on a statistical threshold, it was in no way influenced by any theoretical position on cerebral asymmetry per se. Her data suggests that 80% (95%

CI 67%, 89%) of her participants had more right-hemispheric activation in response to faces. Her lab also suggests that test-retest asymmetry for faces is quite reliable, at least in right-handed individuals (Yovel et al., 2008). Rossion and colleagues suggest roughly 75% of right handers from Rossion et al. (2012) are right lateralized (Bukowski et al., 2013). A similar estimate is also available from the Auckland laboratory (Badzakova-Trajkov et al., 2010), suggesting an even more dramatic breadth of right hemispheric dominance in right handers (90%, although the dynamic face stimuli they used may depend on a more anterior network of regions in the temporal lobe than the static face images we used in this study; see Pitcher et al., 2019).

Unfortunately, unlike in the aphasia literature, there are no equivalent estimates of prosopagnosia incidence after unilateral left or right brain damage for right handers (let alone for non-right handed groups). Therefore, different neuroimaging techniques can only be compared to one another as evidence for validity of the particular technique (or to behavioural literature such as chimeric face bias, meta-analysed in Karlsson et al., 2019). Nevertheless, if threshold-independent techniques are used, other types of face-related fMRI activity using different localizers should provide estimates of degree of asymmetry for different components of the core and extended face networks (e.g. Bukowski et al., 2013; Frässle et al., 2016; Zhen et al., 2015). This issue will be explored in further detail, along with the body asymmetry data displayed in Fig. 3, in a subsequent report.

3.2. Reliability

The significant correlations for all three tasks were higher than expected, given there was little opportunity to control participants' alertness, strategy and performance, in particular for our sub-vocal verbal fluency task, where it is not possible to control that participants were performing as requested. The visual localizers, developed by colleagues for group-average threshold dependent purposes, may not have been of optimal length for reliable quantification in individual people. Nevertheless, the current results are encouraging for researchers who want to quantify cerebral asymmetries using threshold-independent techniques such as the Wilke and Lidzba (2007) LI toolbox. (In fact, the estimates and their distribution etc. could be compared with other-threshold independent techniques, such as the iBrain™ procedures developed by Abbott et al., 2010. A few papers have reported more than one measure on the same datasets, see for example Ocklenburg et al., 2013, others reviewed in Bradshaw et al., 2017a, 2017b). The current data adds to this evidence base, which suggests relatively stable asymmetries in individual adult brains. In fact, we are particularly encouraged by the suggestion that the reliability is not appreciably lower in non-right handers or in groups with the atypical dominance in question.

These correlational/classification results are quite noteworthy, as they are obtained from relatively short samples of BOLD signal. For the fluency task, data was collected in two 7-min experiment runs, with only 210 s thinking of words (the others being equally occupied by the control task RARA/LALA, versus rest). We also randomly assigned specific letters to run 1 and run 2, which could have added some noise to our estimates in some of the participants, although to date there is little evidence to speak to item difficulty and lateralization in verbal fluency (see Amunts et al., 2004, and Shao et al., 2014, for discussion of phonological versus executive/semantic processes in fluency). For faces and bodies, two 6-min runs included these visual stimulus types as well as chairs and scenes were presented, along with five rest periods. In other words, much like for fluency, the actual "time on task" for each visual attribute was 128 s. Undoubtedly more stimulus processing time would refine the LIs we obtained here considerably. A composite LI from the two runs is likely to be a better estimate than either single one alone, in all likelihood.

Run 1- run 2 reliabilities might overestimate reliability, as they avoid additional sources of noise that are added if actual test-retest imaging

sessions can be performed (for example, state-dependent fluctuations in BOLD, participant alertness, strategy, etc). LIs from fTCD have higher split-half reliabilities (Wilson and Bishop, 2018) than test-retest (Woodhead et al., 2019), although that technique depends quite heavily on signal quality from the placements of the probes, so could underestimate reliability relative to fMRI. We have some test-retest data on 21 of our participants, who returned for a second test session which included one 7-letter block of verbal fluency. This test-retest correlation ($r = .94$) is very similar to that obtained in our run 1- run 2 comparison, but more participants with intermediate language LIs would firm up this estimate (see scatterplot of these two LIs in supplementary materials). These data also suggest the utility of verbal fluency as a measure of language lateralization.

For our body and face tasks, the relevant subtraction condition for each attribute might also have considerable effect on obtained LIs. There is a surprisingly small literature on this sort of question in face processing research; none of which has focussed on estimates of cerebral asymmetry per se. We followed convention of our face perception colleagues here and subtracted scenes from faces (Kanwisher and Yovel, 2006) and chairs from bodies (Downing et al., 2007; Taylor et al., 2007). If the question of interest was to compare the depth and breadth of these asymmetries with one another directly, a standardized subtraction stimulus category could be desirable (in fact we find that in LIs calculated with the task compared to rest are highly correlated with the subtraction-based LIs). If within-task split-half or test-retest correlations, or, for example, across group comparisons (handedness, sex, typical versus atypical laterality) of frequencies are the key question, this consideration is probably less important.

In spite of these concerns, our language task was the most robust on a very important metric: no right-handers and only two left-handers were classified as left hemispheric for one of the runs and right hemispheric for the other. The robustness of the run 1 - run 2 correlation works for people with right hemisphere dominance (the lower left quadrant of Fig. 1, effectively) for language, a group for which considerably more variability may have resulted (given weaker asymmetries and more heterogeneity, in group studies, at least). The face perception task had a higher proportion of hemispheric "switch", with three right-handers and 12 left-handers changing direction across the runs. Five right handers and 13 left handers changed the direction of their asymmetry for body processing (many of these people with different side of asymmetry in the two runs are unique for each asymmetry: one non-right-handed person was inconsistent for fluency and faces but not bodies. Three individuals, one right-handed and two non-right-handed, were inconsistent for both faces and bodies, but no participants for all three measures).

An average of both runs, compared to a later retest of two runs of the same localizer in the same people might produce fewer incongruences than we have found here (our retest data mentioned above includes only one run resulting in incongruent classification in 1/21 people). An alternative might be to screen out some of the individuals with weak asymmetry. Large studies of this sort could be used to develop data-driven rules for, hopefully, a small band of individuals with LIs sufficiently close to 0 that certainty of direction of laterality cannot be established (Carey and Karlsson, 2019).

Such screening could, in theory, reduce misclassification rates by using a trichotomous scheme, which would include a bilateral/no asymmetry category, centred on an LI of 0. The dilemma for such a procedure is how to select how large such a boundary would be, although a data-driven approach based on data from an independent study or studies is one sensible option (Vingerhoets, 2019a). We instead favour the transparency of a dichotomous classification scheme centred on zero (see Carey and Karlsson, 2019). Of course, other laboratories are free to re-analyse the current data using their own trichotomous scheme of choice as we have provided the raw data in scatterplots and in supplementary materials in a spreadsheet table. We would recommend this as standard practice in future, given the importance of proportions of individuals who show typical and atypical asymmetries for any function

(Vingerhoets, 2019b).

Individuals who are less lateralized on a particular function are in some sense the most important to study, at the very least to quantify as fully as possible the distribution of the cerebral asymmetry in question (for example, the full distribution bimodal, trimodal, or unimodal, shifted towards typical LIs has considerable theoretical implication - see Mazoyer et al., 2014, for an excellent example of full distributions of language LIs as a function of handedness group). Our results do suggest for fluency and bodies in particular, that these data may be remarkably skewed in right handers at least, so finding sufficient numbers of weakly and/or atypically-lateralized people to fully characterise those distributions is a challenge. Any models of cerebral dominance, handedness, and/or hemispheric specialization have to include rarer, atypical individuals for good statistical as well as theoretical reasons. The threshold-independent techniques here seem appropriate for comparing different asymmetries in the same individuals.

For non-language related functions, there is even less relevant work to date, although some recent work on faces (Badzakova-Trajkov et al., 2010; Bukowski et al., 2013; Gerrits et al., 2019), and attention (Badzakova-Trajkov et al., 2010; Cai et al., 2013) in recent years is encouraging. Asymmetries related to the right hemisphere have been largely ignored by handedness researchers (reviewed in Karlsson et al., 2019). It is very tempting to implicitly assume that all cerebral asymmetries depend, albeit to varying degrees, on language. In this view, other asymmetries, especially ones favouring the right hemisphere, are a secondary consequence of language. Some evidence to date already suggests that right hemispheric dominance for attention is statistically unrelated to left hemispheric dominance for language (Karlsson et al., 2019). Asymmetries are by definition binary – many which favour a particular hemisphere could be completely independent of one another in terms of magnitude, localization, and any underlying genetic determinant. Bryden (1990) suggested that, in contrast to a causal relationship between typical asymmetries in the left and right hemispheres, many asymmetries might only be coincidental; no one ever yolks left localization of the heart to left hemispheric specialization for speech, in spite of their congruence in most people. To establish which cerebral asymmetries relate to one another and which ones do not, a programme of measuring the magnitude of several cerebral asymmetries *in the same people* is called for. The current data suggest that this enterprise is challenging, but doable, and well worth the while.

Disclosure of interest

The authors report no conflict of interest.

CRediT authorship contribution statement

Leah T. Johnstone: Formal analysis, Writing - original draft. **Emma M. Karlsson:** Writing - original draft, Visualization. **David P. Carey:** Conceptualization, Writing - original draft, Funding acquisition.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.neuropsychologia.2020.107331.

References

Abbott, D.F., Waites, A.B., Lillywhite, L.M., Jackson, G.D., 2010. fMRI assessment of language lateralization: an objective approach. Neuroimage 50 (4), 1446–1455. https://doi.org/10.1016/j.neuroimage.2010.01.059.

Adcock, J.E., Wise, R.G., Oxbury, J.M., Oxbury, S.M., Matthews, P.M., 2003. Quantitative fMRI assessment of the differences in lateralization of language-related brain activation in patients with temporal lobe epilepsy. Neuroimage 18 (2), 423–438. https://doi.org/10.1016/S1053-8119(02)00013-7.

Amunts, K., Weiss, P.H., Mohlberg, H., Pieperhoff, P., Eickhoff, S., Gurd, J.M., et al., 2004. Analysis of neural mechanisms underlying verbal fluency in cytoarchitectonically defined stereotaxic space—the roles of Brodmann areas 44 and 45. Neuroimage 22 (1), 42–56. https://doi.org/10.1016/j.neuroimage.2003.12.031.

Badzakova-Trajkov, G., Corballis, M.C., Häberling, I.S., 2016. Complementarity or independence of hemispheric specializations? A brief review. Neuropsychologia 93B, 386–393. https://doi.org/10.1016/j.neuropsychologia.2015.12.018.

Badzakova-Trajkov, G., Häberling, I.S., Roberts, R.P., Corballis, M.C., 2010. Cerebral asymmetries: complementary and independent processes. PLoS One 5 (3), e9682. https://doi.org/10.1371/journal.pone.0009682.

Baynes, K., Long, D.L., 2007. Three conundrums of language lateralization. Lang. Linguist. Compass 1 (1-2), 48–70. https://doi.org/10.1111/j.1749-818X.2007.00006.x.

Berl, M.M., Zimmaro, L.A., Khan, O.I., Dustin, I., Ritzl, E., Duke, E.S., Sepeta, L.N., Sato, S., Theodore, W.H., Gaillard, W.D., 2014. Characterization of atypical language activation patterns in focal epilepsy. Ann. Neurol. 75 (1), 33–42. https://doi.org/10.1002/ana.24015.

Biduła, S.P., Przybylski, Ł., Pawlak, M.A., Króliczak, G., 2017. Unique neural characteristics of atypical lateralization of language in healthy individuals. Front. Neurosci. 11, 525. https://doi.org/10.3389/fnins.2017.00525.

Binder, J.R., Swanson, S.J., Hammeke, T.A., Morris, G.L., Mueller, W.M., Fischer, M., et al., 1996. Determination of language dominance using functional MRI: a comparison with the Wada test. Neurology 46 (4), 978–984. https://doi.org/10.1212/WNL.46.4.978.

Boles, D.B., 1996. Factor analysis and the cerebral hemispheres: "Unlocalized" functions. Neuropsychologia 34 (7), 723–736. https://doi.org/10.1016/0028-3932(95)00136-0.

Bradshaw, A.R., Bishop, D.V., Woodhead, Z.V., 2017a. Methodological considerations in assessment of language lateralization with fMRI: a systematic review. PeerJ 5, e3557. https://doi.org/10.7717/peerj.3557.

Bradshaw, A.R., Thompson, P.A., Wilson, A.C., Bishop, D.V., Woodhead, Z.V., 2017b. Measuring language lateralization with different language tasks: a systematic review. PeerJ 5, e3929. https://doi.org/10.7717/peerj.3929.

Brain, W.R., 1945. Speech and handedness. Lancet 246 (6383), 837–842. https://doi.org/10.1016/S0140-6736(45)91573-X.

Bryden, M.P., 1965. Tachistoscopic recognition, handedness, and cerebral dominance. Neuropsychologia 3, 1–8. https://doi.org/10.1016/0028-3932(65)90015-1.

Bryden, M.P., 1982. Laterality: Functional Asymmetry in the Intact Brain. Academic Press, New York.

Bryden, M.P., 1990. Choosing sides: the left and right of the normal brain. Can. Psychol. 31, 297–309. https://doi.org/10.1037/h0078949.

Bukowski, H., Dricot, L., Hanseeuw, B., Rossion, B., 2013. Cerebral lateralization of face-sensitive areas in left-handers: only the FFA does not get it right. Cortex 49 (9), 2583–2589. https://doi.org/10.1016/j.cortex.2013.05.002.

Cai, Q., Van der Haegen, L., 2015. What can atypical language hemispheric specialization tell us about cognitive functions? Neurosci. Bull. 31 (2), 220–226. https://doi.org/10.1007/s12264-014-1505-5.

Cai, Q., Van der Haegen, L., Brysbaert, M., 2013. Complementary hemispheric specialization for language production and visuospatial attention. Proc. Natl. Acad. Sci. 110 (4), E322–E330. https://doi.org/10.1073/pnas.1212956110.

Carey, D.P., Johnstone, L.T., 2014. Quantifying cerebral asymmetries for language in dextrals and adextrals with random-effects meta analysis. Front. Psychol. 5, 1128. https://doi.org/10.3389/fpsyg.2014.01128.

Carey, D.P., Karlsson, E.M., 2019. A bright future for the study of multiple cerebral asymmetries? Comment on "Phenotypes in hemispheric functional segregation? Perspectives and challenges" by Guy Vingerhoets. Phys. Life Rev. 30, 19–21. https://doi.org/10.1016/j.plrev.2019.08.009.

Chen, E.E., Small, S.L., 2007. Test–retest reliability in fMRI of language: group and task effects. Brain Lang. 102 (2), 176–185. https://doi.org/10.1016/j.bandl.2006.04.015.

Chilosi, A.M., Comparini, A., Cristofani, P., Turi, M., Berrettini, S., Forli, F., et al., 2014. Cerebral lateralization for language in deaf children with cochlear implantation. Brain Lang. 129, 1–6. https://doi.org/10.1016/j.bandl.2013.12.002.

Corbetta, M., Miezin, F.M., Dobmeyer, S., Shulman, G.L., Petersen, S.E., 1990. Attentional modulation of neural processing of shape, color, and velocity in humans. Science 248 (4962), 1556–1559. https://doi.org/10.1126/science.2360050.

Deppe, M., Knecht, S., Papke, K., Lohmann, H., Fleischer, H., Heindel, W., et al., 2000. Assessment of hemispheric language lateralization: a comparison between fMRI and fTCD. J. Cereb. Blood Flow Metab. 20 (2), 263–268. https://doi.org/10.1097/00004647-200002000-00006.

Desmond, J.E., Sum, J.M., Wagner, A.D., Demb, J.B., Shear, P.K., Glover, G.H., et al., 1995. Functional MRI measurement of language lateralization in Wada-tested patients. Brain 118 (6), 1411–1419. https://doi.org/10.1093/brain/118.6.1411.

Downing, P.E., Wiggett, A.J., Peelen, M.V., 2007. Functional magnetic resonance imaging investigation of overlapping lateral occipitotemporal activations using multi-voxel pattern analysis. J. Neurosci. 27 (1), 226–233. https://doi.org/10.1523/JNEUROSCI.3619-06.2007.

Duchaine, B., Yovel, G., 2015. A revised neural framework for face processing. Annu. Rev. Vis. Sci. 1, 393–416. https://doi.org/10.1146/annurev-vision-082114-035518.

Elias, L.J., Bryden, M.P., Bulman-Fleming, M.B., 1998. Footedness is a better predictor than is handedness of emotional lateralization. Neuropsychologia 36 (1), 37–43. https://doi.org/10.1016/S0028-3932(97)00107-3.

Fesl, G., Bruhns, P., Rau, S., Wiesmann, M., Ilmberger, J., Kegel, G., Brueckmann, H., 2010. Sensitivity and reliability of language laterality assessment with a free reversed association task-a fMRI study. Eur. Radiol. 20 (3), 683–695. https://doi.org/10.1007/s00330-009-1602-4.

Frässle, S., Paulus, F.M., Krach, S., Schweinberger, S.R., Stephan, K.E., Jansen, A., 2016. Mechanisms of hemispheric lateralization: asymmetric interhemispheric recruitment in the face perception network. Neuroimage 124, 977–988. https://doi.org/10.1016/j.neuroimage.2015.09.055.

Gazzaniga, M.S., Hillyard, S.A., 1971. Language and speech capacity of the right hemisphere. Neuropsychologia 9 (3), 273–280. https://doi.org/10.1016/0028-3932(71)90022-4.

Gelinas, J.N., Fitzpatrick, K.P., Kim, H.C., Bjornson, B.H., 2014. Cerebellar language mapping and cerebral language dominance in pediatric epilepsy surgery patients. Neuroimage: Clinical 6, 296–306. https://doi.org/10.1016/j.nicl.2014.06.016.

Gerrits, R., Van der Haegen, L., Brysbaert, M., Vingerhoets, G., 2019. Laterality for recognizing written words and faces in the fusiform gyrus covaries with language dominance. Cortex 117, 196–204. https://doi.org/10.1016/j.cortex.2019.03.010.

Gobbini, M.I., Haxby, J.V., 2007. Neural systems for recognition of familiar faces. Neuropsychologia 45 (1), 32–41. https://doi.org/10.1016/j.neuropsychologia.2006.04.015.

Goldenberg, G., 2013. Apraxia: the Cognitive Side of Motor Control. Oxford University Press, Oxford.

Gregory, R.L., 1961. The brain as an engineering problem. In: Thorpe, W.H., Zangwill, O.L. (Eds.), Current Problems in Animal Behavior. University Press, Cambridge, pp. 307–330.

Guenther, F.H., Hickok, G., 2016. Neural models of motor speech control. In: Hickok, G., Small, S.L. (Eds.), Neurobiology of Language. Academic Press, Amsterdam, pp. 725–740.

Häberling, I.S., Corballis, M.C., 2016. Cerebellar asymmetry, cortical asymmetry and handedness: two independent networks. *Laterality: Asymmetries of Body*. Brain Cogn. 21 (4–6), 397–414. https://doi.org/10.1080/1357650X.2015.1110161.

Häberling, I.S., Corballis, P.M., Corballis, M.C., 2016a. Language, gesture, and handedness: evidence for independent lateralized networks. Cortex 82, 72–85. https://doi.org/10.1016/j.cortex.2016.06.003.

Häberling, I.S., Steinemann, A., Corballis, M.C., 2016b. Cerebral asymmetry for language: comparing production with comprehension. Neuropsychologia 80, 17–23. https://doi.org/10.1016/j.neuropsychologia.2015.11.002.

Harrington, G.S., Buonocore, M.H., Farias, S.T., 2006. Intrasubject reproducibility of functional MR imaging activation in language tasks. Am. J. Neuroradiol. 27 (4), 938–944.

Hickok, G., Poeppel, D., 2007. The cortical organization of speech processing. Nat. Rev. Neurosci. 8 (5), 393. https://doi.org/10.1038/nrn2113.

Hunter, Z.R., Brysbaert, M., 2008. Visual half-field experiments are a good measure of cerebral language dominance if used properly: evidence from fMRI. Neuropsychologia 46 (1), 316–325. https://doi.org/10.1016/j.neuropsychologia.2007.07.007.

Janecek, J.K., Swanson, S.J., Sabsevitz, D.S., Hammeke, T.A., Raghavan E., M., Rozman, M., Binder, J.R., 2013. Language lateralization by fMRI and Wada testing in 229 patients with epilepsy: rates and predictors of discordance. Epilepsia 54 (2), 314–322. https://doi.org/10.1111/epi.12068.

Jansen, A., Flöel, A., Van Randenborgh, J., Konrad, C., Rotte, M., Förster, A.F., et al., 2005. Crossed cerebro–cerebellar language dominance. Hum. Brain Mapp. 24 (3), 165–172. https://doi.org/10.1002/hbm.20077.

Jansen, A., Menke, R., Sommer, J., Förster, A.F., Bruchmann, S., Hempleman, J., et al., 2006. The assessment of hemispheric lateralization in functional MRI—robustness and reproducibility. Neuroimage 33 (1), 204–217. https://doi.org/10.1016/j.neuroimage.2006.06.019.

Joliot, M., Tzourio-Mazoyer, N., Mazoyer, B., 2016. Intra-hemispheric intrinsic connectivity asymmetry and its relationships with handedness and language lateralization. Neuropsychologia 93, 437–447. https://doi.org/10.1016/j.neuropsychologia.2016.03.013.

Kanwisher, N., 2010. Functional specificity in the human brain: a window into the functional architecture of the mind. Proc. Natl. Acad. Sci. 107 (25), 11163–11170. https://doi.org/10.1073/pnas.1005062107.

Kanwisher, N., McDermott, J., Chun, M.M., 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J. Neurosci. 17 (11), 4302–4311. https://doi.org/10.1523/JNEUROSCI.17-11-04302.1997.

Kanwisher, N., Yovel, G., 2006. The fusiform face area: a cortical region specialized for the perception of faces. Philos. Trans. R. Soc. Biol. Sci. 361 (1476), 2109–2128. https://doi.org/10.1098/rstb.2006.1934.

Karlsson, E.M., Johnstone, L.T., Carey, D.P., 2019. The depth and breadth of multiple perceptual asymmetries in right handers and non-right handers. Laterality: Asymmetries Body Brain Cogn. 24 (6), 707–739. https://doi.org/10.1080/1357650X.2019.1652308.

Kimura, D., 1983. Speech representation in an unbiased sample of left-handers. Hum. Neurobiol. 2 (3), 147–154.

Knecht, S., Dräger, B., Deppe, M., Bobe, L., Lohmann, H., Flöel, A., Ringelstein, E.B., Henningsen, H., 2000. Handedness and hemispheric language dominance in healthy humans. Brain 123 (12), 2512–2518. https://doi.org/10.1093/brain/123.12.2512.

Levy, J., Heller, W., Banich, M.T., Burton, L.A., 1983. Asymmetry of perception in free viewing of chimeric faces. Brain Cogn. 2 (4), 404–419. https://doi.org/10.1016/0278-2626(83)90021-0.

Liegeois, F., Connelly, A., Salmond, C.H., Gadian, D.G., Vargha-Khadem, F., Baldeweg, T., 2002. A direct test for lateralization of language activation using fMRI: comparison with invasive assessments in children with epilepsy. Neuroimage 17 (4), 1861–1867. https://doi.org/10.1006/nimg.2002.1327.

Mazoyer, B., Mellet, E., Perchey, G., Zago, L., Crivello, F., Jobard, G., et al., 2016. BIL&GIN: a neuroimaging, cognitive, behavioral, and genetic database for the study of human brain lateralization. Neuroimage 124, 1225–1231. https://doi.org/10.1016/j.neuroimage.2015.02.071.

Mazoyer, B., Zago, L., Jobard, G., Crivello, F., Joliot, M., Perchey, G., et al., 2014. Gaussian mixture modelling of hemispheric lateralization for language in a large sample of healthy individuals balanced for handedness. PLoS One 9 (6), e101165. https://doi.org/10.1371/journal.pone.0101165.

McCarthy, G., Puce, A., Gore, J.C., Allison, T., 1997. Face-specific processing in the human fusiform gyrus. J. Cogn. Neurosci. 9 (5), 605–610. https://doi.org/10.1162/jocn.1997.9.5.605.

Morrison, M.A., Churchill, N.W., Cusimano, M.D., Schweizer, T.A., Das, S., Graham, S.J., 2016. Reliability of task-based fMRI for preoperative planning: a test-retest study in brain tumor patients and healthy controls. PLoS One 11 (2), e0149547. https://doi.org/10.1371/journal.pone.0149547.

Ocklenburg, S., Beste, C., Arning, L., Peterburs, J., Güntürkün, O., 2014. The ontogenesis of language lateralization and its relation to handedness. Neurosci. Biobehav. Rev. 43, 191–198. https://doi.org/10.1016/j.neubiorev.2014.04.008.

Ocklenburg, S., Hugdahl, K., Westerhausen, R., 2013. Structural white matter asymmetries in relation to functional asymmetries during speech perception and production. Neuroimage 83, 1088–1097. https://doi.org/10.1016/j.neuroimage.2013.07.076.

Peelen, M.V., Wiggett, A.J., Downing, P.E., 2006. Patterns of fMRI activity dissociate overlapping functional brain areas that respond to biological motion. Neuron 49 (6), 815–822. https://doi.org/10.1016/j.neuron.2006.02.004.

Petersen, S.E., Fox, P.T., Posner, M.I., Mintun, M., Raichle, M.E., 1988. Positron emission tomographic studies of the cortical anatomy of single-word processing. Nature 331 (6157), 585. https://doi.org/10.1038/331585a0.

Piervincenzi, C., Petrilli, A., Marini, A., Caulo, M., Committeri, G., Sestieri, C., 2016. Multimodal assessment of hemispheric lateralization for language and its relevance for behavior. Neuroimage 142, 351–370. https://doi.org/10.1016/j.neuroimage.2016.08.018.

Pitcher, D., Ianni, G., Ungerleider, L.G., 2019. A functional dissociation of face-, body-and scene-selective brain areas based on their response to moving and static stimuli. Sci. Rep. 9 (1), 8242. https://doi.org/10.1038/s41598-019-44663-9.

Powell, J.L., Kemp, G.J., García-Fiñaña, M., 2012. Association between language and spatial laterality and cognitive ability: an fMRI study. Neuroimage 59 (2), 1818–1829. https://doi.org/10.1016/j.neuroimage.2011.08.040.

Rasmussen, T., Milner, B., 1977. The role of early left-brain injury in determining lateralization of cerebral speech functions. Ann. N. Y. Acad. Sci. 299 (1), 355–369. https://doi.org/10.1111/j.1749-6632.1977.tb41921.x.

Rossion, B., Hanseeuw, B., Dricot, L., 2012. Defining face perception areas in the human brain: a large-scale factorial fMRI face localizer analysis. Brain Cogn. 79 (2), 138–157. https://doi.org/10.1016/j.bandc.2012.01.001.

Rutten, G.J.M., Ramsey, N.F., Van Rijen, P.C., Van Veelen, C.W.M., 2002. Reproducibility of fMRI-determined language lateralization in individual subjects. Brain Lang. 80 (3), 421–437. https://doi.org/10.1006/brln.2001.2600.

Seghier, M.L., 2008. Laterality index in functional MRI: methodological issues. Magn. Reson. Imag. 26 (5), 594–601. https://doi.org/10.1016/j.mri.2007.10.010.

Seghier, M.L., Lazeyras, F., Pegna, A.J., Annoni, J.M., Zimine, I., Mayer, E., et al., 2004. Variability of fMRI activation during a phonological and semantic language task in healthy subjects. Hum. Brain Mapp. 23 (3), 140–155. https://doi.org/10.1002/hbm.20053.

Shao, Z., Janse, E., Visser, K., Meyer, A.S., 2014. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. Front. Psychol. 5, 772. https://doi.org/10.3389/fpsyg.2014.00772.

Somers, M., Neggers, S.F., Diederen, K.M., Boks, M.P., Kahn, R.S., Sommer, I.E., 2011. The measurement of language lateralization with functional transcranial Doppler and functional MRI: a critical evaluation. Front. Hum. Neurosci. 5, 31. https://doi.org/10.3389/fnhum.2011.00031.

Springer, J.A., Binder, J.R., Hammeke, T.A., Swanson, S.J., Frost, J.A., Bellgowan, P.S., Brewer, C.C., Perry, H.M., Morris, G.L., Mueller, W.M., 1999. Language dominance in neurologically normal and epilepsy subjects: a functional MRI study. Brain 122 (11), 2033–2046. https://doi.org/10.1093/brain/122.11.2033.

Steenhuis, R.E., Bryden, M.P., 1989. Different dimensions of hand preference that relate to skilled and unskilled activities. Cortex 25 (2), 289–304. https://doi.org/10.1016/S0010-9452(89)80044-9.

Stroobant, N., Vingerhoets, G., 2000. Transcranial Doppler ultrasonography monitoring of cerebral hemodynamics during performance of cognitive tasks: a review. Neuropsychol. Rev. 10 (4), 213–231. https://doi.org/10.1023/A:1026412811036.

Tailby, C., Abbott, D.F., Jackson, G.D., 2017. The diminishing dominance of the dominant hemisphere: language fMRI in focal epilepsy. Neuroimage: Clinical 14, 141–150. https://doi.org/10.1016/j.nicl.2017.01.011.

Taylor, J.C., Wiggett, A.J., Downing, P.E., 2007. Functional MRI analysis of body and body part representations in the extrastriate and fusiform body areas. J. Neurophysiol. 98 (3), 1626–1633. https://doi.org/10.1152/jn.00012.2007.

Van der Haegen, L., Brysbaert, M., 2018. The relationship between behavioral language laterality, face laterality and language performance in left-handers. PLoS One 13 (12), e0208696. https://doi.org/10.1371/journal.pone.0208696.

Van der Haegen, L., Cai, Q., Brysbaert, M., 2012. Colateralization of Broca's area and the visual word form area in left-handers: fMRI evidence. Brain Lang. 122, 171–178. https://doi.org/10.1016/j.bandl.2011.11.004.

Van der Haegen, L., Cai, Q., Seurinck, R., Brysbaert, M., 2011. Further fMRI validation of the visual half field technique as an indicator of language laterality: a large-group analysis. Neuropsychologia 49 (10), 2879–2888. https://doi.org/10.1016/j.neuropsychologia.2011.06.014.

Vingerhoets, G., 2019a. Phenotypes in hemispheric functional segregation? Perspectives and challenges. Phys. Life Rev. 30, 1–18. https://doi.org/10.1016/j.plrev.2019.06.002.

Vingerhoets, G., 2019b. Toward a multidimensional description of individual variation in hemispheric functional segregation: reply to comments on "Phenotypes in hemispheric functional segregation? Perspectives and challenges". Phys. Life Rev. 30, 41–46. https://doi.org/10.1016/j.plrev.2019.10.011.

Vingerhoets, G., Alderweireldt, A.-S., Vandemaele, P., Cai, Q., Van der Haegen, L., Brysbaert, M., Achten, E., 2013. Praxis and language are linked: evidence from co-lateralization in individuals with atypical language dominance. Cortex 49, 172–183. https://doi.org/10.1016/j.cortex.2011.11.003.

Wegrzyn, M., Mertens, M., Bien, C.G., Woermann, F.G., Labudda, K., 2019. Volume-wise analysis of fMRI time series allows accurate prediction of language lateralization. BioRxiv 725671. https://doi.org/10.1101/725671.

Westerhausen, R., Kompus, K., Hugdahl, K., 2014. Mapping hemispheric symmetries, relative asymmetries, and absolute asymmetries underlying the auditory laterality effect. Neuroimage 84, 962–970. https://doi.org/10.1016/j.neuroimage.2013.09.074.

Whitehouse, A.J., Bishop, D.V., 2009. Hemispheric division of function is the result of independent probabilistic biases. Neuropsychologia 47 (8), 1938–1943. https://doi.org/10.1016/j.neuropsychologia.2009.03.005.

Wilke, M., Lidzba, K., 2007. LI-tool: a new toolbox to assess lateralization in functional MR-data. J. Neurosci. Methods 163 (1), 128–136. https://doi.org/10.1016/j.jneumeth.2007.01.026.

Wilke, M., Schmithorst, V.J., 2006. A combined bootstrap/histogram analysis approach for computing a lateralization index from neuroimaging data. Neuroimage 33 (2), 522–530. https://doi.org/10.1016/j.neuroimage.2006.07.010.

Willems, R.M., Van der Haegen, L., Fisher, S.E., Francks, C., 2014. On the other hand: including left-handers in cognitive neuroscience and neurogenetics. Nat. Rev. Neurosci. 15 (3), 193–201. https://doi.org/10.1038/nrn3679.

Wilson, A.C., Bishop, D.V., 2018. Resounding failure to replicate links between developmental language disorder and cerebral lateralisation. PeerJ 6, e4217. https://doi.org/10.7717/peerj.4217.

Woermann, F.G., Jokeit, H., Luerding, R., Freitag, H., Schulz, R., Guertler, S., Okujava, M., Wolf, P., Tuxhorn, I., Ebner, A., 2003. Language lateralization by Wada test and fMRI in 100 patients with epilepsy. Neurology 61 (5), 699–701. https://doi.org/10.1212/01.WNL.0000078815.03224.57.

Woodhead, Z.V.J., Bradshaw, A.R., Wilson, A.C., Thompson, P.A., Bishop, D.V., 2019. Testing the unitary theory of language lateralization using functional transcranial Doppler sonography in adults. Royal Soc. Open Sci. 6 (3), 181801. https://doi.org/10.1098/rsos.181801.

Woodhead, Z.V., Rutherford, H.A., Bishop, D.V., 2018. Measurement of language laterality using functional transcranial Doppler ultrasound: a comparison of different tasks. Wellcome Open Res. 3 https://doi.org/10.12688/wellcomeopenres.14720.2.

Yovel, G., Tambini, A., Brandman, T., 2008. The asymmetry of the fusiform face area is a stable individual characteristic that underlies the left-visual-field superiority for faces. Neuropsychologia 46 (13), 3061–3068. https://doi.org/10.1016/j.neuropsychologia.2008.06.01.

Zago, L., Petit, L., Mellet, E., Jobard, G., Crivello, F., Joliot, M., et al., 2016. The association between hemispheric specialization for language production and for spatial attention depends on left-hand preference strength. Neuropsychologia 93, 394–406. https://doi.org/10.1016/j.neuropsychologia.2015.11.018.

Zangwill, O.L., 1960. Cerebral Dominance and its Relation to Psychological Function. Oxford, England.

Zhen, Z., Yang, Z., Huang, L., Kong, X.Z., Wang, X., Dang, X., et al., 2015. Quantifying interindividual variability and asymmetry of face-selective regions: a probabilistic functional atlas. Neuroimage 113, 13–25. https://doi.org/10.1016/j.neuroimage.2015.03.010.