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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 localised 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 = .89 to r = .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.

## Keywords: laterality, brain asymmetry, test-retest, fMRI, language dominance, face perception, body perception

Cerebral dominance, in our species at least, was a central research theme in behavioural neurology and neuropsychology for much of the 20<sup>th</sup> 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, Miezin, Dobmeyer, Shulman, & Petersen, 1990; Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Gore, & Allison, 1997; Petersen, Fox, Posner, Mintun, & Raichle, 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 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 lateralised for speech/ language functions, however these are assessed (Bryden, 1982; Carey & Johnstone, 2014; Gazzaniga & Hillyard, 1971; Rasmussen & Milner, 1977). To add to this state of affairs, handedness, relevant in a rather complex way to the rarer kinds of cerebral asymmetry (Baynes & Long, 2007; Elias, Bryden, & Bulman-Fleming, 1998; Gerrits, Van der Haegen, Brysbaert, & Vingerhoets, 2019; Joliot, Tzourio-Mazoyer, & Mazoyer, 2016; Levy, Heller, Banich, & Burton, 1983; Ocklenburg, Beste, Arning, Peterburs, & Güntürkün, 2014; Willems, Van der Haegen, Fisher, & Francks, 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, Häberling, Roberts, & Corballis, 2010; Carey & Johnstone, 2014; Mazoyer et al., 2014; Rasmussen & Milner, 1977; Whitehouse & 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, Corballis, & Häberling, 2016; Cai & Van der Haegen, 2015; Goldenberg, 2013; Hunter & Brysbaert, 2008; Mazoyer et al., 2016; Van der Haegen & Brysbaert, 2018; Van der Haegen, Cai, & Brysbaert, 2012; Vingerhoets, 2019; 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 specialisation (Karlsson, Johnstone, & Carey, 2019; Van der Haegen & 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 neuroimaging, 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, Abbott, & Jackson, 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 yaxis of the activated voxels in one of the two hemispheres. By overlaying 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, Kompus, and Hugdahl (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, Waites, Lillywhite, & Jackson, 2010; Adcock, Wise, Oxbury, Oxbury, & Matthews, 2003; Liegeois et al., 2002; Seghier, 2008; Wilke & Lidzba, 2007; reviewed in Bradshaw, Bishop, & Woodhead, 2017).

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., 2017) is implemented in an SPM toolbox (Wilke & Lidzba, 2007; see also Wilke & 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: Badzakov-Trajov et al., 2010; Häberling, Corballis, & Corballis, 2016; Bordeaux: Mazoyer et al., 2016; Zago et al., 2016; and Ghent: Cai, Van der Haegen, & Brysbaert, 2013; Van der Haegen, Cai, Seurinck, & 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 & 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, Ramsey, Van Rijen, & Van Veelen, 2002). Two exceptions from fMRI needs mentioning here: Harrington, Buonocore, and Farias (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 testretest 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; Zangwill, 1960; reviewed in Carey & 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 exploit ed.

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, Przybylski, Pawlak, & Króliczak, 2017; Häberling, Steinemann, & Corballis, 2016; Hunter & Brysbaert, 2008; Powell, Kemp, & García-Finaña, 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, Wiggett, & Peelen, 2007; Peelen, Wiggett, & Downing, 2006).

#### Methods

#### **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 (> 4mm). The right handed subjects had a mean age of 26.09 (SD = 5.92) and a mean Waterloo handedness questionnaire (WHQ; Steenhuis, & Bryden, 1989: -30 most left, to +30 most 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).

#### Language task

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 seconds. 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.

#### 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 seconds 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.

#### fMRI acquisition

All scans were acquired in a Philips 3 Tesla Achieva magnetic resonance (MR) 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 x 220, acquisition matrix = 96 x 96, 36 slices were acquired; acquired voxel size (mm) =  $2.3 \times 2.3 \times 2.5$  (reconstructed voxel size (mm) =  $2.3 \times 2.3 \times 2.5$ ). 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 magnetisation. High resolution T1-weighted structural images were obtained with the following parameters: T1-weighted image acquisition TR = 12 ms, TE = 3.5 ms, FA =  $8^\circ$ , FOV (mm) =  $240 \times 240$ , acquisition matrix =  $80 \times 79$ ; 175 contiguous slices were acquired, voxel size (mm) =  $1 \times 1 \times 2$  (reconstructed voxel size =  $1 \text{ mm}^3$ ).

#### **Design and analysis**

All MRI data were pre-processed and analyzed using SPM12 (Wellcome of Department 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 (3mm 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 & Lidzba, 2007; Wilke & 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 & 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 string, faces > scenes, and bodies > chairs. The latter two are regularly used in the FFA and EBA literature (Downing, Wiggett, & Peelen, 2007; Taylor, Wiggett, & Downing, 2010). 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, Fitzpatrick, Kim, & Bjornson, 2014; Häberling, & 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.

#### Results

#### Language localiser

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 Figure 1). A significant correlation was found when comparing the LIs from run 1 with those from run 2 (r = .92, p < .001,  $r^2 = .85$ ; 95% CI .88, .95). LIs across runs were compared for right handed and non-right handed samples separately, resulting in equivalently strong correlations for both groups (r = .84, p < .001, 95% CI = .70, .92, and r = .92, p < .001, 95% CI = .87, .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 = .60, p < .001, 95% CI = .43, .73; atypicals: r = .77, p < .001; 95% CI = .46, .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.



Figure 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 subjects, and red datapoints represent non-right handed subjects. 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.

#### **Face localiser**

Six right handed and 11 non-right handed participants changed the direction of their asymmetry across the two runs of this task. 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 = .72, p < .001,  $r^2 = .52$ , 95% CI = .60, .81). LIs across runs were compared for right handed and non-right handed samples separately, resulting in strong correlations for both groups (r = .59, p < .001, 95% CI = .31, .78; and r = .76, p < .001, 95% CI = .63, .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 = .35, p = .006, 95% CI = .10, .56) and those with atypical face dominance (r = .42, p = .016, 95% CI = .08, .67).



<u>Figure 2</u> – Scatterplot of the LI scores across the two runs of the face localiser task. It is likely that the increased number of participants in the upper-left and bottom-right

quadrants as compared with the language localiser data is due to the decrease in power obtained across these runs.

#### **Body Localiser**

Twenty participants, 6 right handed and 14 non-right handed, changed the direction of their asymmetry across the two runs of this task. 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 = .62, p < .001,  $r^2 = .38$ ; 95% CI = .48, .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 = .63, p < .001, 95% CI = .45, .76), but not right handed participants (r = .29, p = .093, 95% CI = -.06, .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 = .26, p = .028,  $r^2 = .07$ , 95% CI = -.03, .47) but not those with atypical dominance (r = .31, p = .163, 95% CI = -.13, .65).



Figure 3 – A scatterplot of the LI scores across the two runs of the body localiser task.

#### 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 & Lidzba, 2007; Wilke & 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).

#### Validity

In our meta-analysis of language dominance (Carey & 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 & 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 & 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 & 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 LI which could be compared to an fMRI-derived LI. Unfortunately, this multiple Wada measure approach has not been standardised or psychometrically assessed (Knecht et al., 1998). fTCD has been used for some years now to quantify magnitude of asymmetry (Stroobant & 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., 2017). 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 lateralised. 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 & Poeppel, 2007; Guenther & 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, Rutherford, & Bishop, 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 specialisation 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 occipitotemporal cortex that are relatively selective for face stimuli (Duchaine & Yovel, 2015; Gobbini & 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 FFA 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 probably quite reliable, at least in right-handed individuals (Yovel, Tambini, & Brandman, 2008). Rossion and colleagues suggest roughly 75% of right handers from Rossion, Hanseeuw, and Dricot (2012) are right lateralised (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, Ianni, & Ungerleider, 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 localisers 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 Figure 2, in a subsequent report.

#### 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<sup>™</sup> procedures developed by Abbott et al., 2010. A few papers have reported more than one measure on the same datasets, see for example Ocklenburg Hugdahl, & Westerhausen, 2013, others reviewed in Bradshaw Thompson, Wilson, Bishop, & Woodhead, 2017). 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 seven-minute experiment runs, with only 210 seconds 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, Janse, Visser, & Meyer, 2014, for discussion of phonological versus executive/semantic processes in fluency). For faces and bodies, two six-minute 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 seconds. 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 & Bishop, 2018) than test-retest (Woodhead, Bradshaw, Wilson, Thompson, & Bishop, 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 laterization.

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 & Yovel, 2006) and chairs from bodies (Downing et al., 2007; Taylor et al., 2010). If the question of interest was to compare the depth and breadth of these asymmetries with one another directly, a standardised 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 figure 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 changed the 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 re-test of two runs of the same localiser in the same people might produce fewer incongruencies than we have found here (our re-test 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 & 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 & Karlsson, 2019). Of course, other laboratories are free to reanalyse 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 lateralised 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-lateralised people to fully characterise those distributions is a challenge. Any models of cerebral dominance, handedness, and/or hemispheric specialisation have to include rarer, atypical individuals for good statistical as well as theoretical reasons. The threshold-dependent 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, localisation, 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 localisation of the heart to left hemispheric specialisation 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.

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Fluency LI frontal lobe mask

Supplementary Figure 1. Verbal fluency whole brain contrast LIs compared with frontal lobe only LIs for all participants. These two different estimates are highly correlated with one another (r = .95).



<u>Supplementary Figure 2</u>. LI's for 21 individuals from the current data set who have subsequently been rescanned as part of a second study which included one block of verbal fluency (7 letters). All but two of these individuals were scanned at least two years later in the one-block fluency task. Estimates from the current study are plotted on the y axis. The correlation may be somewhat elevated by the two clusters of data and appears to be more convincing in the language atypicals (lower left quadrant). Nevertheless 20/21 individuals are classified congruently.



<u>Supplementary Figure 3</u>. Verbal fluency LIs as a function of Waterloo Handedness Questionnaire Score (-30 complete left preference; +30 complete right preference).



<u>Supplementary Figure 4</u>. Face LIs as a function of Waterloo Handedness Questionnaire Score.



<u>Supplementary Figure 5</u>. Body LIs as a function of Waterloo Handedness Questionnaire Score.