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MEASURING NATURAL HEMISPHERIC ASYMMETRY IN THE BRAIN: QUANTIFYING THE YAKOVLEVIAN TORQUE PHENOMENON

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Essay/Thesis:	30 hp
Program and/or course:	Medical physics
Level:	Second cycle
Semester/year:	Spring 2020
Supervisor:	Rolf A. Heckemann
Examiner:	Magnus Båth

Abstract

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Background:
Just by a cursory examination, the two hemispheres of the human brain may appear as mirror images of one another. Yet, the left and right sides exhibit profound differences in anatomy. One of the most obvious expressions of hemispheric asymmetry is the counterclockwise rotation of the brain known as "Yakovlevian torque".

Objective:
To measure natural hemispheric asymmetry in the brain by studying the involvement of individual regions in the Yakovlevian torque.

Method:
Asymmetry was studied on T1-weighted whole-brain atlases of 285 healthy study participants, each labeling 83 anatomical structures. Three techniques were employed: visual scoring, ordinary volumetric asymmetry, and an advanced registration-based technique proposed by Martinez-Torteya et al. [2019].

Results:
Regionally specific differences between the two hemispheres were evident in all investigated regions, with particularly large asymmetry indices found for the temporal horn of the lateral ventricle, the pre-subgenual frontal cortex, and the lateral orbital gyrus. Asymmetry indices obtained from the registration-based measure were higher than the volume measures for 78% of the region pairs. The visual scoring corresponded well with these results but was possibly confounded by differences between the data sets.

Conclusion:
This study illustrates the distribution of structural asymmetries in the healthy human brain. Automatic quantification of the brain torque was proven more challenging than anticipated, as the investigation did not lead to a suitable method. Moreover, volumetric assessment of asymmetry should be complemented with an index that is also sensitive to shape.

Contents

1 Introduction

Natural hemispheric asymmetry is a well-known aspect of human brain organization. For more than a century, studies have demonstrated asymmetries in both function and structure between the two halves of our brain; from language skills to gyral and sulcal variation. According to Toga and Thompson [2003], these are thought to reflect evolutionary, hereditary, developmental, experiential, and pathological factors. One of the earliest observations of functional asymmetry was made in the nineteenth century when pioneering work by Broca [1861], followed by Wernicke and Lichtheim [1874], showed that damage to specific areas of the left hemisphere would cause deficits in the production and comprehension of language. Similarly, subsequent research showed that visuospatial abilities and social understanding are represented more strongly in the right hemisphere [Sperry et al., 1979]; [Sperry, 1982]; [Heilman and Abell, 1980]; [Mort and Kennard, 2003].

Historically, hemispheric asymmetry was considered a uniquely human trait and even that which distinguished us as a species. In contrast to this view, modern research shows that left-right asymmetries of brain and behaviour are widespread in the animal kingdom [LeMay, 1976]; [Bisazza et al., 1998]; [Corballis, 2009]. Comparative studies on non-human primates even suggest that some of them may have evolved together before chimpanzees (Pan troglodytes) and humans diverged, while others arose independently after the evolutionary split some five to six million years ago [Hopkins, 2013]. An example of this is a pronounced leftward asymmetry of the planum temporale (PT), which has been documented in both the human and chimpanzee brain, albeit to a lower degree in the latter [Geschwind and Levitsky, 1968]; [Hopkins et al., 1998]. The PT forms the core of Wernicke's language comprehension area, and it is commonly believed that the expansion of this region gave rise to our superior language skills and a left hemispheric dominance for language [Spocter et al., 2010]; [Gannon et al., 1998]; [Foundas et al., 1994].

Having the two sides of our brain specialize in complementary functions has been argued to enhance neural efficiency. By allocating specific tasks to each hemisphere, separate functions can be carried out simultaneously without costly interference or useless duplication of neural circuitry [Ringo et al., 1994]; [Rogers et al., 2004]. As suggested by Palmer [2004], bilateral symmetry can be considered the default condition of humans and other bilaterian animals; being defined about an anteroposterior and dorsoventral axis during development. Yet symmetry is repeatedly broken, not the least by the way our brain perceives and responds to stimuli, thus implying adaptive advantages in lateralization. These departures from symmetry occur both at the individual level, as so-called fluctuating asymmetries, and at the population level with most individuals showing similar direction of bias. This widespread pattern has long puzzled researchers as individual brain efficiency does not require asymmetries to be aligned in a population. Lateral biases in perception or overt behaviour might even be disadvantageous as it makes individual behaviour more predictable to predators. Theoretical models on the evolution of lateralization suggest that the alignment of the direction of behavioural and brain asymmetries among vertebrates and invertebrates may have evolved under “social” selection pressures when individually asymmetric organisms had to coordinate their behaviour with each other. The evolutionary and developmental pathways leading to lateralization may therefore reflect a trade-off between the relative costs and benefits of symmetry and asymmetry [Vallortigara and Rogers, 2005].

When it comes to structure, the human brain hemispheres are strikingly similar in almost every respect. Nonetheless they also display some important anatomical differences [Amunts, 2010]. Among the most prominent features of hemispheric asymmetry are the right frontal and left occipital *petalia*. The petalias are local impressions on the inner surface of the skull caused by the relative protrusions of the hemispheres. A related finding is the frequent extension of the right frontal and left occipital lobes over the midline (onto their respective counterparts) [LeMay, 1976]; [Toga and Thompson, 2003]. Since the warping of the lobes is usually more pronounced in the posterior aspect, the effect has been termed *occipital bending*. In the 1960’s, Yakovlev and Rakic [1966] described the overall asymmetry as looking like somebody had taken the brain between two hands and torqued it slightly. Thus, the phenomenon has become known as “Yakovlevian torque”.

With X-ray computed tomography (CT) or structural magnetic resonance (MR) imaging, we are able to characterize macrostructural asymmetries *in vivo* [Amunts, 2010]. While most of these are present in the majority of people, in some individuals they are absent or even reversed [Corballis, 2009]. Brain asymmetry studies accumulated over the past decades have evidenced that the variability in brain asymmetry is influenced by various biological factors, such as age, sex, handedness, and disease. For instance, atypical asymmetry has been related to numerous psychiatric and neurodevelopmental disorders, including dyslexia [Eckert, 2004], Alzheimer’s Disease (AD) [Heckemann et al., 2011]; [Thompson et al., 1998], attention-deficit/hyperactivity disorder (ADHD) [Shaw et al., 2009], Autism Spectrum Disorder (ASD) [Postema et al., 2019], psychotic disorders [Crow, 1990]; [Okada et al., 2016], and mood disorders [Yucel et al., 2009]; [Drevets et al., 1997]. Measuring natural asymmetry thereby affords compelling opportunities to characterize abnormalities or idiosyncrasies of individual development. Further, by quantifying asymmetry at a healthy stage we can better understand how the anatomy of our brain may be alterered in disease. This could eventually help elucidate the progression of pathological conditions and provide new or potentially replace current biomarkers with more sensitive ones.

A wide range of measurement techniques has previously been used to investigate regional differences between the two hemispheres, including various aspects of the torque. However, these have relied mainly on volume measures of the cerebral cortex or a limited selection of subcortical structures [Lyttelton et al., 2009]; [Szabó et al., 2003]. More recently, Martinez-Torteya et al. [2019] proposed a registration-based approach for measuring hippocampal neuroanatomical asymmetry, resulting in a shape-based asymmetry measure that may be a more accurate marker of AD than current volumetric markers. While their asymmetry measure was proven more indicative of AD than left hippocampal volume, the area under the curve in the receiver-operating characteristics test did not suggest that it was useful as a biomarker by itself. Bakidou [2019] later reproduced the results of Martinez-Torteya et al. [2019] and extended the work by studying mild cognitive impairment (MCI) in addition to AD, and the amygdala in addition to the hippocampus. She showed that amygdalar symmetry is affected by the disease to a similar degree as the hippocampus, and concluded that AD has a biological effect that is measurable as asymmetry.

The technique used in these investigations has shown great potential in assessing neuroanatomical asymmetry. A logical next step is therefore to apply the technique to other brain regions. In this study, I aimed to measure the natural hemispheric asymmetry in the healthy human brain by implementing the method proposed by Martinez-Torteya et al. [2019]. I sought to identify the contribution of individual cortical and subcortical structures to the Yakovlevian torque phenomenon. In addition, I compared the sensitivity of the shape-based asymmetry index proposed by Martinez-Torteya et al. [2019] with plain volumetric asymmetry.

2 Method

2.1 Data acquisition and image preprocessing

The data used in this paper were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) and consisted of TI-weighted screening (1.5 T) and baseline (3 T) MR images of 285 healthy elderly study participants. The ADNI was launched in 2003 as a public-private partnership. The primary goal of ADNI has been to test whether serial MR imaging, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

Automatic whole-brain segmentations for the MRI data were also available from the ADNI database and had been generated using multi-atlas propagation with enhanced registration (MAPER), rendering labels for 83 anatomical regions, including 40 left/right pairs [Heckemann et al., 2010, 2011].

2.2 Asymmetry measurements

Inter-hemispheric asymmetry was measured in 40 bilaterally paired brain regions by employing the methodology proposed by Martinez-Torteya et al. [2019]. All processing steps described below were performed in Bash (Unix shell), utilizing software tools retrieved from the Medical Image Registration ToolKit (MIRTK, [Schuh et al., 2018]). First, left and right hemispheric structure labels were extracted from the segmentation images using the *calculate-element-wise* function. Then *flip-image* was used to reflect left hemispheric labels, individually, about the mid-sagittal plane so that they would have the same orientation as their right homologue. A rigid registration (6 degrees of freedom; i.e. 3 rotations and 3 translations) was then carried out between both label images. This was done with the *register* function, optimizing for the sum of squared differences with a gradient descent to yield the alignment with maximum overlap. Lastly, neuroanatomical asymmetry, α, was calculated from the aligned label pair using the *evaluate-overlap* tool, according to

$$\alpha = 1 - \frac{V_r + V_l - V_\Delta}{V_r + V_l} \tag{1}$$

where V_l and V_r are the number of voxels of the left and right brain regions, respectively, and V_Δ is the number of voxels that did not overlap. Complete overlap between two structures would lead to an α value of zero.

Regional volume asymmetry was derived by computing an asymmetry index (AI) following the formula

$$\mathrm{AI} = 2 \cdot \frac{\mid V_r - V_l \mid}{V_r + V_l} \tag{2}$$

where V_l and V_r refer, as above, to the number of voxels of the left and right hemispheric brain regions. AI measured zero when $V_l = V_r$. The AI is a widely used index in brain asymmetry studies. Also note that neither index scales with l, r, or overall brain size, owing to the denominators.

The sensitivity of α and AI was compared by calculating the rank difference for each region. The raw values of both indices were converted into ranking positions, where a greater difference in rank implies a weaker agreement between metrics.

The evaluation of asymmetry measurements was performed in R version 4.0.0.

2.3 Visual scoring

To analyze the agreement between measurements and visual perception of asymmetry, differences in shape and volume between corresponding structures were evaluated subjectively and rated. The scores were defined on a three-point scale as follows

1. No visible *or* weak asymmetry
2. Moderate asymmetry
3. Strong asymmetry

The data set used for the visual scoring was the Hammers Atlas Database, consisting of 30 individual brain atlases with 83 manually drawn regions each. Details of the acquisition are in Hammers et al. [2003]. Segmentation protocols used in the preparation of resulted labels are described in Hammers et al. [2003] and Gousias et al. [2008] and are available at www.brain-development.org. All scans were viewed in MRIcron, a cross-platform Neuroimaging Informatics Technology Initiative (NIfTI) format image viewer developed by Rorden et al. [2007]. The individual scores assigned to each region pair were averaged across participants.

3 Results

3.1 Asymmetry measurements

From 285 participants and 40 region pairs, I obtained 11 385 plausible measurements. Failures (no result or $\alpha = 1$) occurred in 15 instances. No attempt was made to rescue these measurements; they were excluded. For the remaining measurements, the range of α was 0.040–0.693, and the range of AI was 0–1.034.

Among the most symmetric regions on both α and AI were the cerebellum, thalamus, and posterior temporal lobe. Particularly strong asymmetry was evident in the temporal horn of the lateral ventricle, the presubgenual frontal cortex, and the lateral orbital gyrus. Asymmetry was also prominent in traditional frontal and temporal language regions in the perisylvian cortex. The two measures diverged strongly on the precentral gyrus (mean $\alpha = 0.168$, mean AI = 0.045, rank difference -20) and the postcentral gyrus (mean $\alpha = 0.196$, mean AI = 0.074, rank difference -18), meaning that for these two region pairs, the volume asymmetry was negligible, but the shape asymmetry was distinct. The opposite finding was evident for the lateral ventricle ($\alpha = 0.144$, AI = 0.147, rank difference 23) and the anterior temporal lobe medial part ($\alpha = 0.137$, AI = 0.103, rank difference 16).

The correlation between measured α and AI values for all region pairs is illustrated in Fig. 1. In general, α showed larger magnitudes of asymmetry compared to AI. Few exceptions were observed in which AI on average depicted larger values than α. This was most apparent in the presubgenual frontal cortex and the lateral ventricle. Moreover, AI generally showed a larger spread of values compared to α, with larger maximum values as a result (Fig. 2).

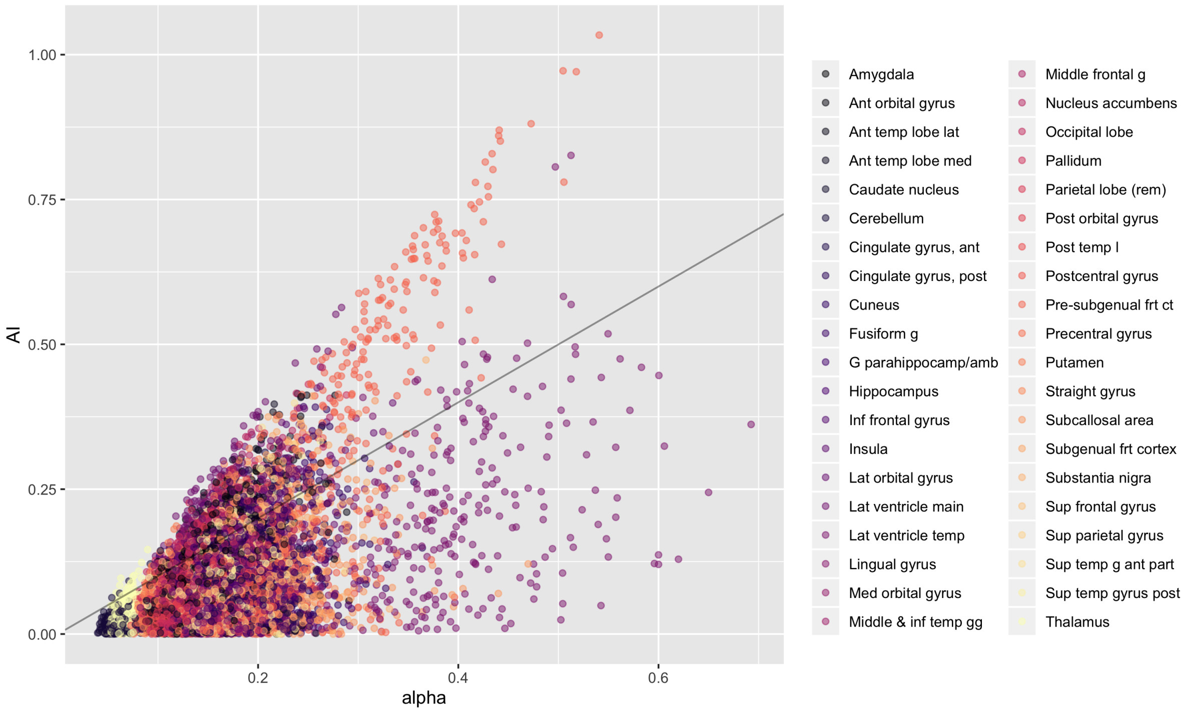


Figure 1: Scatter plot of α (alpha) versus AI for each region pair. Colours correspond to a specific brain structure. Each point in the plot represents a pair of measurements for each participant. The identity line is showed in black.

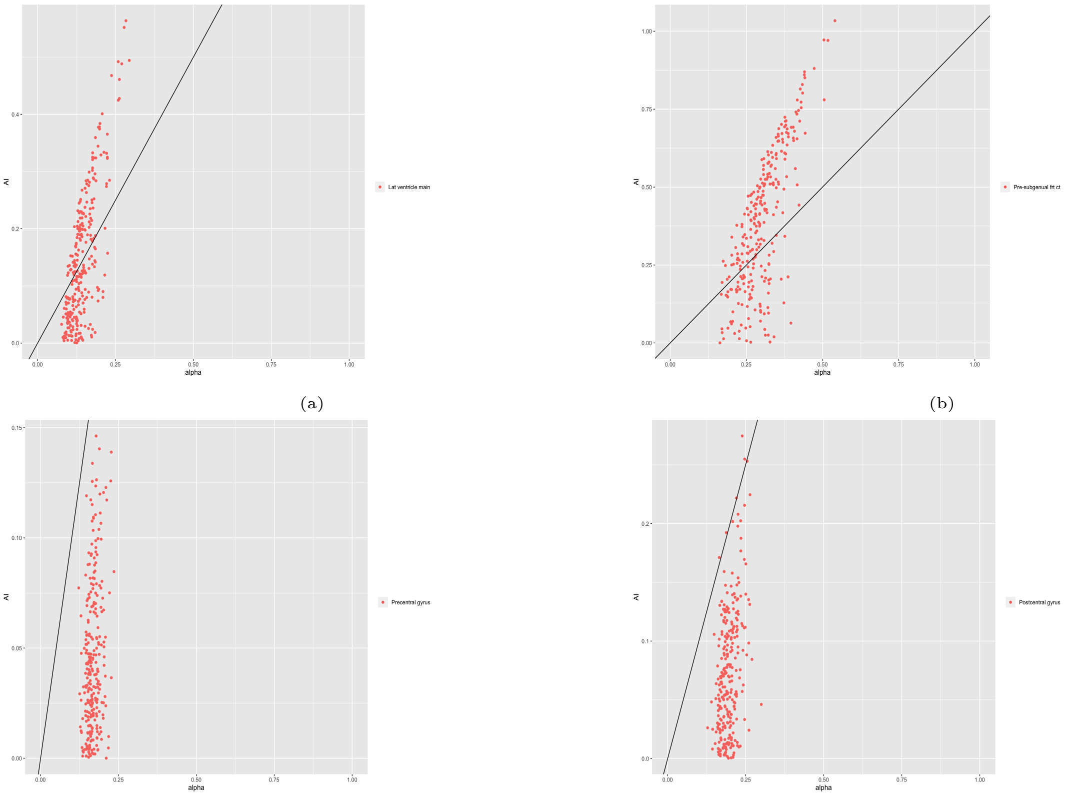
Table 1 shows for all region pairs the robust maximum of α and AI as an indicator of the amplitude of the respective index value and a comparison index. Values were on average higher according to α than AI for most (31/40) of the regions.

3.2 Visual scoring

The visual scoring showed good agreement with asymmetry measurements. However, larger cortical structures (e.g. the occipital and posterior temporal lobe) tended to receive a high score considering α, while smaller structures (e.g. the subcallosal area and the temporal horn of the lateral ventricle) were assigned low scores. Fig. 3 shows the distribution of measured α values for all region pairs, where the colouring under the curves represents the averaged scoring results.

Table 1: Comparison of α and AI as asymmetry indices. Robust maximum (90th percentile) and a difference index are shown. Rows are arranged in descending order of the absolute value of the difference index. Positive difference values (31/40) indicate stronger sensitivity of α, negative difference values (9/40) indicate stronger sensitivity of AI.

	Pair name	α	AI	Difference
1	Insula	0.16	0.06	92
2	Cerebellum	0.07	0.03	73
3	Precentral gyrus	0.19	0.09	70
4	Sup frontal gyrus	0.17	0.10	54
5	Pre-subgenual frt ct	0.39	0.68	-53
6	Substantia nigra	0.24	0.14	53
7	Postcentral gyrus	0.23	0.14	51
8	Sup parietal gyrus	0.16	0.09	51
9	Middle frontal g	0.16	0.10	48
10	Med orbital gyrus	0.19	0.12	45
11	Lat ventricle main	0.19	0.30	-43
12	G parahippocamp/amb	0.19	0.13	40
13	Post temp l	0.13	0.09	39
14	Cingulate gyrus, post	0.19	0.13	34
15	Subcallosal area	0.31	0.22	33
16	Lingual gyrus	0.22	0.16	30
17	Post orbital gyrus	0.19	0.15	27
18	Caudate nucleus	0.17	0.14	23
19	Nucleus accumbens	0.21	0.27	-23
20	Ant temp lobe med	0.17	0.21	-22
21	Lat ventricle temp	0.51	0.41	22
22	Straight gyrus	0.19	0.24	-21
23	Cingulate gyrus, ant	0.23	0.19	19
24	Parietal lobe (rem)	0.14	0.12	18
25	Putamen	0.13	0.11	18
26	Cuneus	0.26	0.22	17
27	Thalamus	0.08	0.07	17
28	Hippocampus	0.21	0.18	15
29	Ant temp lobe lat	0.23	0.27	-14
30	Subgenual frt cortex	0.24	0.28	-14
31	Middle & inf temp gg	0.16	0.18	-13
32	Pallidum	0.18	0.15	13
33	Fusiform g	0.24	0.21	12
34	Inf frontal gyrus	0.19	0.18	8
35	Sup temp g ant part	0.21	0.20	7
36	Ant orbital gyrus	0.17	0.17	3
37	Lat orbital gyrus	0.26	0.27	-3
38	Occipital lobe	0.14	0.14	2
39	Amygdala	0.17	0.17	1
40	Sup temp gyrus post	0.21	0.21	1



(a) (b) (c) (d)

Figure 2: Scatter plots of α (alpha) versus AI for regions (a) lateral ventricle, (b) presubgenual frontal cortex, (c) precentral gyrus, (d) postcentral gyrus. Each point represents a pair of measurements for each participant.

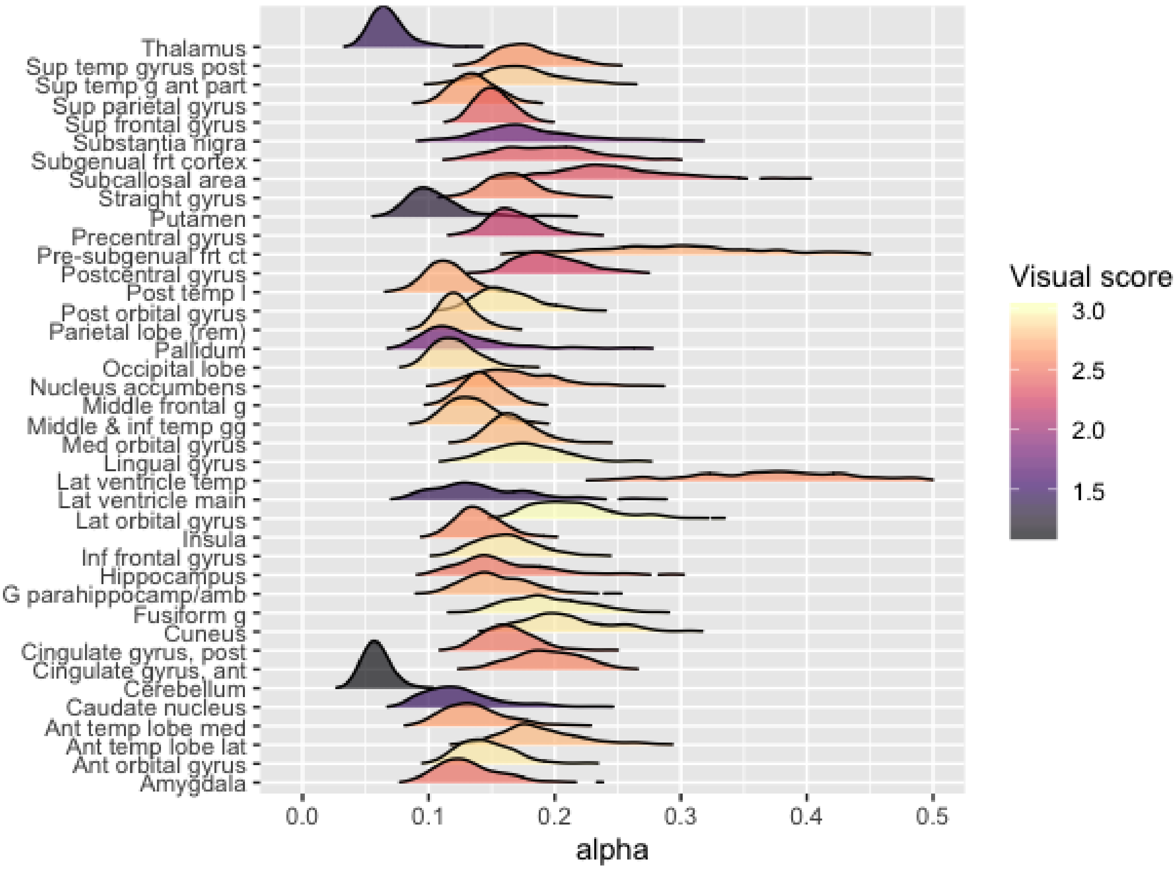


Figure 3: Distribution of measured asymmetry values (alpha) for each individual region pair. Colours correspond to visual assessment of asymmetry. Warmer colours (towards yellow) indicate a higher score, cooler colours (towards gray) indicate a lower score.

4 Discussion

In this study, left and right hemispheric regions were compared in healthy individuals using two metrics, one volume-based and one shape-based. The goal was to establish which cerebral regions tend to be asymmetrical in the general population and to what degree. Traditionally, research regarding this topic has focused on studying the influences of factors like age and sex on brain structure [Guadalupe et al., 2017]; [Wang et al., 2019]. Others have been in clinical contexts, comparing asymmetry patterns attributed to certain neurological and psychiatric conditions [Kong et al., 2018b]. However, findings have often been contradictory, likely due to methodological differences between studies as well as insufficient sample sizes in relation to subtle effects [Kong et al., 2018a]; [Biberacher et al., 2016]. Recently, automated segmentation methods and publicly available brain atlases have facilitated large-scale studies of the brain, where harmonized protocols and procedures have been used to eliminate inconsistencies [Petersen et al., 2010]; [Heckemann et al., 2010]; [Hammers et al., 2003].

4.1 Correspondence with Previous Findings

Inter-hemispheric differences were found in a large number of regions, including the frontal and occipital cortices, which are particularly affected by the petalias and overall brain torque [Toga and Thompson, 2003]. Related to this, I also noticed strong asymmetry in the perisylvian regions, specifically in the inferior frontal and superior temporal gyrus. These results corroborate previous findings, e.g. [Good et al., 2001]; [Delisi et al., 1994]; [Kong et al., 2018b].

The perisylvian area contains both Broca's speech and Wernicke's receptive language areas [Catani et al., 2005]; [Rentería, 2012]. It also encompasses the Sylvian fissure (SF); one of the first anatomical asymmetries described in humans [Geschwind and Levitsky, 1968]. In most individuals, the left SF is significantly longer than the right. Furthermore, in both fetal and adult brains, the posterior end of the right SF is commonly higher than the left, an asymmetrical shift caused by the torque. Accompanying these features is also a typically larger left planum temporale [LeMay, 1976]. Evidence for perisylvian asymmetry has been consistently observed in non-human primates as well, though directional biases are more pronounced in humans [Liu and Phillips, 2009]. Less than a century ago, researchers were convinced that hemispheric asymmetry was restricted to the human brain. However, this idea is being increasingly refuted by the diverse findings in animal species [Corballis, 2008]; [Ocklenburg and Güntürkün, 2012]. Some of them parallel those documented in humans, providing further support of their gradual evolution [Hopkins, 2013]; [Hopkins et al., 2015]; [Gannon et al., 2005]; [Spocter et al., 2010].

Leftward functional and morphological asymmetry in language-related regions has been widely reported in the literature [Niznikiewicz, 2000]; [Good et al., 2001]; [Chiarello et al., 2013]; [Reynolds et al., 2019]. Both the inferior frontal gyrus (containing Broca's area) and the anterior and posterior part of the superior temporal gyrus (containing Wernicke's area) have received particular attention in the context of language lateralization in the past [Reynolds et al., 2019]; [Foundas et al., 1996]; [Foundas et al., 1998]. Findings in these regions might correlate with the documented left-hemispheric dominance for language [Price, 2000]. Another brain region that has been linked to language functions is the insular cortex (or insula for short). For instance, Biduła and Króliczak [2015] reported that the left insula is implicated in gestural language, and Oh et al. [2014] showed that speech production and language processing involve activation of distinct insular subregions.

I found strong asymmetry in several key regions for visuospatial processing, such as the fusiform gyrus, cuneus, and lingual gyrus. Most previous studies have shown a rightward trend in these regions, consistent with the widely-held view that visuospatial attention is processed mainly in the right hemisphere [Kong et al., 2018b]; [Luders et al., 2006]; [Plessen et al., 2014]. Additional findings in the pre-/ and postcentral gyrus, anterior temporal and superior parietal lobes are in line with those reported by Luders et al. [2006] and Plessen et al. [2014]. The precentral gyrus is known as the primary motor cortex. In an early investigation of motor cortex asymmetries in relation to handedness, Amunts et al. [1996] showed that in right-handed individuals, the left central sulcus was deeper than the right, and vice versa for left-handed individuals. In addition, their findings suggested that handedness was associated with increased connectivity and intrasulcal surface of the precentral gyrus in the dominant hemisphere. Steinmetz et al. [1991] also reported that PT asymmetry was correlated with hand dominance, with right-handed individuals showing greater leftward PT asymmetry compared to left-handed individuals.

Handedness and language are perhaps the two most obvious manifestations of cerebral asymmetry in humans. A significant majority of individuals show a left-hemisphere dominance for language and speech. Correspondingly, most people prefer to use their right hand for various activities, which is also regulated by the left hemisphere. Initially, this led to the belief that the left side of our brain was dominant, whereas the right was nondominant (even being referred to as the “minor” hemisphere). However, we now know that the right hemisphere is specialized in complementary functions, such as perception and emotion [Silberman and Weingartner, 1986]; [Corballis, 2003]. There have been conflicting reports, though, on whether handedness really does have an impact on brain asymmetry, or if it merely reflects one [Corballis, 2009]. In a recent large-scale study by the ENIGMA-Laterality Working Group [Kong et al., 2018b], effects of age, sex, and intracranial volume were found. However they found no significant associations regarding handedness.

I also found striking asymmetries in the limbic cortices or structures that are intimately connected to it, including the cingulate cortex, hippocampus, amygdala, and subgenual frontal cortices. The limbic system is responsible for our emotional responses and social behaviours [Devinsky et al., 1995]; [Okada et al., 2016]. It is also involved in higher mental functions such as learning and memory formation. Abnormalities in these regions have often been recognised in mood disorders and schizophrenia [Drevets et al., 1997]. Moreover, both the hippocampus and amygdala are known to show early signs of atrophy in MCI and AD [Martinez-Torteya et al., 2019]; [Ledig et al., 2018]. An important motivation behind large cohort studies like ADNI (which provided the core data set used in the present study) is to discover AD biomarkers that enable accurate diagnosis and can serve as surrogate endpoints in trials of disease-modifying drugs. Current biomarkers include change in amygdalar and hippocampal volumes based on structural MRI [Klein-Koerkamp et al., 2014]; [Ledig et al., 2018].

Interestingly, asymmetry was evident in the insular cortex. As mentioned earlier, the insula is involved in various language tasks [Chiarello et al., 2013]. However, it also has reciprocal connections with the limbic system and subserves a wide variety of functions ranging from sensory and affective processing to decision-making, empathy and emotional processing, proprioception and self-awareness, and motor control [Gogolla, 2017]; [Mutschler et al., 2009]. Several studies have investigated structural and functional correlates of insular asymmetry and found that the anterior insula plays a major role in high-level cognitive control and attentional processes (Menon and Uddin [2010]; Nelson et al. [2010]) as well as experiencing and interpreting social emotions (Lamm and Singer [2010]), while posterior regions are more involved in sensorimotor functions and pain perception [Uddin et al., 2017]. Decreased functional connectivity in the left anterior insula has also been highlighted in major depressive disorder [Veer et al., 2010]. Further, Takahashi et al. [2010] reported that atypical insular morphometry, i.e. reduced gray matter volume in the left anterior insula, is evident in individuals with both current and past major depression.

4.2 Asymmetry Indices

Overall, α produced higher amplitudes of asymmetry compared to AI, especially in the lower ranges where AI indicated little or no asymmetry for several regions (Fig.1). This could indicate that α is more sensitive to neuroanatomical asymmetry than AI, which is plausible as α is sensitive to shape and volume differences, whereas AI only considers volume. Furthermore, if different subregions within a given structure are asymmetrical in opposite directions (i.e. rightward and leftward), the delta-voxels will likely cancel each other out and thus misestimate the 'real' asymmetry. In the case of α, however, this effect would not be as easily overlooked. The advantage of α over conventional volume measures becomes even more important when studying brain diseases, since focal abnormalities are more likely than physiological differences to manifest as shape asymmetry. However, when studying global asymmetries, i.e. processess which affect the brain as a whole, volumetry would suffice, as regional shape might not be affected as strongly as regional volume.

I should also like to emphasize that shape-aware asymmetry measures could strongly improve the statistical power of this type of study, i.e. more subtle biological effects would be detectable with the same number of study participants, or, equivalently, fewer participants would be needed to test a hypothesis about an effect of a given estimated size.

4.3 Visual Scoring

The visual asymmetry scoring corresponded well with measurements of α, although for some regions asymmetry was either overestimated or underestimated in comparison. Interestingly, regions that were most asymmetrical according to α were generally underestimated. For example, this was observed for the subgenual prefrontal cortex, subcallosal area, substantia nigra, and temporal horn of the lateral ventricle. Larger cortical structures, on the other hand, were generally overestimated, such as posterior temporal lobe, parietal lobe (remainder), occipital lobe, and anterior orbital gyrus.

A plausible explanation for this would be that even subtle structural differences are visually more perceptible in larger structures than in smaller ones and would therefore result in a higher score. There might also be more uncertainty for smaller structures owing to limitations in the spatial resolution of MR images. Additional discrepancies may be due to the fact that two different data sets of different sizes were used for the asymmetry measurements and visual scoring. Further, the mean ages of study participants differed between the two data sets, and it is well established that human brain asymmetry changes across the lifespan [Kong et al., 2020]; [Guadalupe et al., 2017]; [Plessen et al., 2014]; [Nie et al., 2013]. Finally, I had no previous experience with evaluating structural brain MR images. Perhaps the scoring results would have looked different if a trained professional had performed the same task.

4.4 Future Analyses

It has been surprisingly difficult to find any clear-cut links between asymmetries and their variability among healthy individuals in the literature. It is clear that brain asymmetry is a multidimensional trait that depends on a complex interplay among several genetic and nongenetic factors. Although our knowledge of human brain organization has increased significantly in recent decades, we are still far from having a complete understanding of the ontogenetic and phylogenetic processes responsible for lateralization. Advances in neuroimaging technology will probably continue to advance this field of research. Current techniques only support the study of gross macrostructural features; more aspects of hemispheric asymmetry could be captured by the integration of different approaches.

The expression of population-level asymmetries (e.g. brain torque and language) has been consistent enough throughout history and across cultures that normal patterns can be mapped, despite individual variations. Findings may then serve as reference data on the typical brain asymmetries in the general population and possibly reveal new avenues to detect and track disease processes. In future work, it would be beneficial to utilize cross-hemispheric registration methods in larger and more varied cohorts to assess neuroanatomical asymmetries within and across groups defined by age, sex, and diagnosis. The relation between structural and functional asymmetries is also understudied and needs further investigation. Another fruitful direction for future research would be to combine neurostructural measures with gene databases to better understand the mechanisms underlying lateralization.

4.5 Potential Limitations

The asymmetry measures presented here make no distinction whether asymmetry is leftward or rightward, but are rather used as an indication of asymmetry strength. This made it difficult to compare my findings with existing literature since most studies have also considered the directionality. However, in this work I aimed to determine the degree and distribution of brain asymmetries. A second objective was to evaluate a promising shape-sensitive measure (α, cf. Section 2.2) by comparison with conventional volume-based asymmetry measures. Both absolute and directional differences between the hemispheres can be extracted from my measurements.

Furthermore, an open question remains with regard to small regions. Discretization into voxels implies that even the plain volume measurement of regions is subject to substantial quantization artefact, if they only consist of a few voxels. It is safe to assume that this problem similarly affects all asymmetry measures discussed here, but the size and consequences of potential misestimations remain to be determined.

5 Conclusion

Several conclusions follow from this study. First, the findings demonstrate that nearly all cerebral regions are asymmetrical on average in the healthy human brain. However, due to its complexity, it is uncertain whether and how the brain torque may play role in my current findings. This could be adressed in the future by a closer examination of components more specific to the torque, such as the frontal/occipital petalias and bending. Second, the registration-based technique used here showed greater sensitivity towards asymmetry than plain volumetry and may provide useful clinical markers. Lastly, the current state of knowledge is largely based on small and methodologically diverse studies. Moving forward, I suggest that brain asymmetries should be analyzed in larger samples than used previously and preferably in combination with functional and genetic data. This would help disentangle the fundaments of hemispheric specialization.

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