Regional differences in human cerebral asymmetries of the human cortical white matter


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ABSTRACT

The form of the structural asymmetries across the cerebral hemispheres, that support well-established functional asymmetries, are not well understood. Although, many previous studies have investigated structural differences in areas associated with strong functional asymmetries, such as language processes, regions of the brain with less well-established functional laterality have received less attention. The current study aims to address this by exploring global white matter asymmetries of the healthy human brain using diffusion tensor imaging (DTI) and tractography. DTI was conducted on twenty-nine healthy right-handed males, and pathways from the four major lobes were reconstructed using probabilistic tractography. Mean FA, parallel and perpendicular diffusion values were calculated and compared across hemispheres for each pathway generated. Significant asymmetries in the parietal (rightward asymmetry) and occipital (leftward asymmetry) pathways were found in FA measures. However, asymmetric patterns in parallel and/or perpendicular diffusion were observed in all four lobes, even in pathways with symmetrical FA. For instance, significant rightward asymmetry in parallel diffusion was found in the parietal and frontal lobes, whereas significant leftward asymmetry was found in the temporal and occipital lobes. We suggest that these different patterns of diffusion asymmetry reflect differences in microanatomy that support the known patterns of differential functional asymmetry. The different directions of anatomical asymmetry support the notion that there may be a number of different lateralisng influences operating in the brain.

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1. Introduction

It is well established that, in humans, each cerebral hemisphere is specialized for particular cognitive processes. Language functions, for example, are predominantly carried out in the left cerebral hemisphere, whereas spatial processing is predominantly performed in the right (Corballis, 1991; McManus, 2002). However, in spite of a staggering amount of research on cerebral lateralisation from a functional perspective, the neuroanatomical characteristics that support it remain obscure. Further, although structural asymmetries have been shown to occur in, for example, the planum temporale (e.g. Chance, Casanova, Switala, & Crow, 2006; Geschwind & Levitsky, 1968), and a general anti-clockwise torque has been proposed (e.g. Crow, 1999; Weinberger, Luchins, Morhia, & Wyatt, 1982), the magnitude of these is not consistently reflected in functional asymmetries.

In perhaps the first systematic attempt at a neuroanatomical explanation for cerebral laterality, Miller (1996) has proposed that the different functional specialisations of the two cerebral hemispheres may be supported by differences in intrahemispheric fibre connectivity. Specifically, he proposed that the right hemisphere has a greater number of fast-conducting cortico-cortical connections, relative to the left hemisphere, which, in contrast, has a greater range of conduction velocities. On this view, the left hemisphere is thus specialised for serial processing in tasks such as language, while the right hemisphere is specialised for parallel processing of spatial information.

In something of a test of this hypothesis, Partadiredja, Miller, and Oorschot (2003) performed a stereotological experiment in rats but found no significant asymmetries in axon morphology in any major lobe. However, the authors noted considerable variation between individual subjects, and individual rats were not tested for functional asymmetries. It is also possible that asymmetries in rats (to the extent they occur) are rather more subtle than those of humans. Therefore, investigations in humans employing a similar broad lobar method are warranted in order to further evaluate Miller’s hypothesis.

Our previous work (Barnett & Kirk, 2005; Iwabuchi & Kirk, 2009; Patston, Kirk, Rolfe, Corballis, & Tippett, 2007; Rolfe, Kirk, & Waldie, 2007), and that of others (e.g. Brown, Larson, & Jeeves, 1994; Ipata, Girelli, Minuissi, & Marzi, 1997; Nowotka & Fersten, 2001; Saron & Davidson, 1989), employing EEG to measure interhemispheric
transfer times (HITT), and thus conduction velocities from cells in the right or left hemisphere, are not inconsistent with Miller’s (1996) hypothesis. That is, the transfer of neural information from cells in the right hemisphere to the left is faster than from those in the left to the right. At least, this is the case for right-handed males. Left-handers (Iwabuchi & Kirk, 2009), females (Nowicka & Friston, 2001), musicians (Patston, Kirk, et al., 2007), as well as those with a variety of neurological disorders (Barnett, Corballis, & Kirk, 2005; Barnett & Kirk, 2005; Rolfe et al., 2007) differ from this general pattern. This fits with numerous reports of less lateralisation in these groups (e.g. Corballis, 1991; Knecht et al., 2000; McManus, 2002; Patston, Corballis, Hogg, & Tippett, 2006; Patston, Hogg, & Tippett, 2007; Potter & Graves, 1988; Shaywitz et al., 1995).

However, these EEG studies measured conduction velocities from cells in the parietal region (see e.g. Iwabuchi & Kirk, 2009), and it remains unclear the degree to which these functional asymmetries are present throughout the brain. Certainly, anatomical asymmetries have been regularly reported, but the majority of these studies have focussed on areas associated with specific functions, usually language. For example, Büchel et al. (2004) and Powell et al. (2006) found greater connectivity in language-related white matter regions in the left hemisphere, namely the arcuate fasciculus, most likely reflecting left hemisphere language dominance. Nevertheless, since the introduction of diffusion tensor imaging (DTI), more global investigations of white matter asymmetries have become possible. For instance, Barrick, Lawes, MacKay, and Clark (2007) discovered asymmetries in the white matter tracts between temporal, frontal and parietal lobes, likely relating to audition, language and attention. Indeed, Liu, Stufflebeam, Sepulcre, Hedden, and Buckner (2009) have found a functional overlap with these findings by locating four independently lateralising factors using resting-state data. Specifically, the factors were found in loci associated with language, visual and attentional functions, as well as internal thought (default network). Therefore a closer inspection of the asymmetries of gross intra-cortical connectivity is warranted.

Despite numerous animal studies highlighting the importance of exploring all diffusion measures in the interpretation of levels of anisotropy (e.g. Beaulieu & Allen, 1994; Schwartz et al., 2005; Takahashi et al., 2002), the majority of research has focused on the measurement of FA, and changes in FA relating to a certain pathology. FA is certainly a valuable measure, but parallel and perpendicular diffusion (calculated from the three eigenvectors) may tell us more about the neural microstructure than FA alone. Parallel diffusion is thought to occur along the length of white matter fibres, while perpendicular diffusion occurs transversely across the fibres. However, one must always consider the fact that these measures originate from molecular diffusion profiles at the resolution of a voxel and do not directly measure white matter fibre structure. That said, these methods can provide very useful information in vivo, in both patient and healthy populations.

As noted above, asymmetries have rarely been investigated globally, and in any case, most studies commonly only report FA, providing only a partial assay of white matter structure. As Beaulieu (2002) points out, two regions possessing the same anisotropy values may have very different underlying diffusion profiles. Therefore, to determine the complete picture of white matter fibre properties, one must also survey the degree of parallel and perpendicular diffusion. Furthermore, Pierpaoli and Basser (1996) point out that two areas with similar anisotropy measures may, depending on the normative values of the area under consideration, contain healthy or damaged tissue. Thus, it is important to gather more extensive knowledge of normal anisotropy values for various white matter regions (e.g. Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999; Liston et al., 2005).

Here we investigate the presence of global asymmetries of white matter in healthy individuals using three measures gathered from DTI and tractography as an attempt to determine the degree of asymmetries in the connections between broad regions of known function, and whether such patterns do indeed follow well-documented functional laterality.

2. Materials and methods

2.1. Data acquisition

Twenty-nine healthy right-handed males with no known history of neurological disease underwent DTI. Age of participants ranged from 19 to 44 years (mean age 27.79 years, SD 7.34). Data were acquired on a 1.5-T Siemens Avanto scanner (Erlangen, Germany) using a single shot spin-echo EPI sequence (TR 9746; TE 101; FOV 256; matrix size 256 × 256; voxel size 2 mm × 2 mm × 2 mm) in 30 non-collinear directions with a diffusion weighting of b = 1000 s/mm² with one scan at b = 0 s/mm². The sequence was applied three times and averaged in order to increase signal to noise ratio. TI-weighted structural volumes were also acquired using 3D MP-RAGE sequence (TR 11; TE 4.94; FOV 256; 176 sagittal slices; matrix size: 256 × 256; voxel size: 1 mm × 1 mm × 1 mm). Acquisition time totalled approximately 15 min. All participants gave informed consent with approval from the University of Auckland Human Participants Ethics Committee.

2.2. Data processing

Diffusion-weighted (DW) data were processed using tools from the FMRIB Software Library (FSL, version 4.1, Oxford Centre for Functional MRI of the Brain (FMRIB), UK; Behrens et al., 2003; Smith et al., 2004; Woolrich et al., 2009]). Using the eddy current correction tool from the FMRIB’s Diffusion Toolbox (FDT, version 2.0), each subject’s data was corrected for eddy current distortions and motion artefacts. We computed FA, mean diffusion (MD) and the three eigenvector maps. Diffusion-weighted images were registered to skull-stripped (using the Brain Extraction Tool) T1 structural image and to a standard MNI brain image using the FMRIB Linear Image Registration Tool. We carried out probabilistic tractography to estimate pathways seeded from the four major lobes (frontal, temporal, parietal and occipital) of each hemisphere which were taken from the Montreal Neurological Institute (MNI) Structural Atlas. Fibre tracking drew 5000 samples from each seed voxel with a step length of 0.5 mm and curvature threshold of 0.2. This generated a connectivity map where each voxel represented a connectivity value where the higher the number, the greater the probability of the pathway passing through that voxel. Due to the non-specific and widespread distribution of connections across the brain, we used a conservative threshold of at least 25% of the maximum samples to ensure the only the inclusion of major tracts with high probability, and to exclude pathways that may be a result of image noise, or had very low probability of actually existing (pathways for each of the four lobes illustrated in Fig. 1). The thresholded connectivity maps were binarised and masked onto the FA, MD and eigenvalue maps to derive mean values for each of the four lobe tracts. The secondary (λ2) and tertiary (λ3) eigenvalues were averaged to provide a value for perpendicular diffusion, while the primary eigenvalue (λ1) was used as an index of parallel diffusion.

2.3. Statistical analysis

FA, MD, parallel and perpendicular diffusion measures were subjected to individual repeated measures ANOVAs with hemisphere (right, left) and lobe (frontal, temporal, parietal and occipital) as within-subject factors. All statistical analyses were performed on SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows and an α level of .05.

3. Results

The repeated measures ANOVAs revealed significant hemisphere by lobe interactions for FA (F(3,384) = 9.12, p < 0.001, corrected using Huynh Feldt). Further post-hoc analysis found significantly greater right than left parietal FA (p < 0.05), greater left than right occipital FA (p < 0.05) and a difference approaching significance of left greater than right temporal FA (p = 0.06). Significant interactions were found for both parallel (F(3,384) = 11.41, p < 0.001, corrected using Greenhouse-Geisser) and perpendicular (F(3,384) = 5.85, p < 0.005, corrected using Huynh Feldt) diffusion. Parallel diffusivity was significantly asymmetrical for all lobes with varying laterality. Frontal and parietal lobes showed a rightward asymmetry (both p < 0.005), while temporal and occipital lobes exhibited asymmetry toward the left (both p < 0.05). Perpendicular
Fig. 1. 3D rendering of thresholded pathways generated from each lobe in one subject superimposed onto a standard brain MNI template (using radiological conventions). Red represents pathways generated from frontal seed masks, yellow from temporal, green from parietal, and blue from occipital. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 2. Bar graphs showing asymmetries in (a) FA, (b) MD, (c) parallel diffusion, and (d) perpendicular diffusion for each of the four lobes (*p < .05; **p < .005).
diffusivities were significantly rightward for frontal (p < 0.05) and occipital (p < 0.005) lobes only. Since no significant interaction was found for MD, we chose not to investigate this any further. Results are illustrated in Fig. 2.

4. Discussion

To the best of our knowledge, we are the first to quantitatively demonstrate significant asymmetries of diffusion properties across each lobe of the human brain, using DTI and probabilistic tractography. We found significant rightward parietal and leftward occipital asymmetries in FA, due to underlying differences in parallel and perpendicular diffusion. A trend toward leftward asymmetry was also seen in the temporal lobes, while frontal lobes did not show any significant interhemispheric differences in FA. There were, however, significant asymmetries in perpendicular diffusion in the occipital and frontal lobes, and significant asymmetries in parallel diffusion across all lobes, with rightward asymmetry in the parietal and frontal, and leftward asymmetry in the temporal and occipital lobes.

In clinical cases, changes in parallel or perpendicular diffusivity are usually interpreted as axonal damage or demyelination respectively (Concha, Gross, Wheatley, & Beaulieu, 2006). However, and obviously, differences between areas of healthy tissue cannot be explained in these terms. Rather, it is likely that such differences are due to variability in the alignment or coherence of fibres, degree of myelination, or axon morphology. The interpretation of DTI parameters, with respect to what they reflect of the underlying fibre properties, is still a matter of some debate (see Discussion in Miller, 2008, pp. 404–405). However, according to Schwartz et al. (2005) perpendicular diffusion is increased with greater axonal spacing, where larger extracellular area allows more diffusion. On the other hand, parallel diffusion was found to positively correlate with axon diameter regardless of myelination. Schwartz et al. (2005) suggests this is likely to be due to decreased cytoskeletal protein density in larger axons, leading to fewer barriers for intracellular diffusion. It has also been reported that an increase in FA in combination with a decrease in perpendicular diffusion is indicative of an increase in myelin (Harsan et al., 2007), since molecules are less able to move perpendicularly to axons in the presence of myelin.

4.1. Parietal asymmetries

The difference in parietal FA seems to be due to the significantly greater parallel diffusion in the right since no significant asymmetry was found here for perpendicular diffusion. This may indicate enhanced coherence of axons in the right parietal relative to the left, and/or greater axonal diameters. Larger axon diameters in the right parietal region relative to the left is consistent with studies showing more rapid right to left interhemispheric transfer than left to right in parietal evoked potentials (Barnett & Kirk, 2005; Brown et al., 1994; Iwabuchi & Kirk, 2009; Marzi, Biciacchi, & Nicoletti, 1991; Nowicka & Fersten, 2001; Patston, Kirk, et al., 2007; Rolfe et al., 2007; Saron & Davidson, 1989), lending some support, at least for the parietal area, for Miller’s (1996) hypothesis of a greater number of faster conducting, myelinated cortico-cortical axons in the right hemisphere. A recent study has in fact revealed rightward asymmetries in pathways connecting the superior parietal lobe with temporal regions (Barrick et al., 2007). This parietal asymmetry may underlie the right hemisphere dominance for both visual (Heilman, Watson, & Valenstein, 1993) and auditory (Petit et al., 2007) attention, and spatial processing in general (Sack et al., 2007), and is also consistent with the rightward asymmetry in the parietal factor in the study by Liu et al. (2009).

4.2. Frontal asymmetries

To highlight the importance of considering all diffusion parameters in studies of this sort, significant frontal asymmetries were seen with both perpendicular and parallel diffusion measures, despite the absence of significant FA asymmetry. The left frontal tracts may contain more myelin than the right and/or have a greater axonal density, while axons in the right frontal pathways may contain a greater number of large-diameter axons combined with a lower axonal density. As with the rightward parietal asymmetry, this rightward frontal asymmetry may reflect the right hemisphere dominance for spatial processing. Indeed, Sack et al. (2007), for example, have proposed that a right lateralised fronto-parietal network is predominantly responsible for visuospatial processing, a general idea that has had previously been suggested on the basis of neuropsychological data (e.g. Mesulam, 1999; Vallar, 1997).

It might have been expected that, given the role of the arcuate fasciculus in fronto-temporal communication during left-lateralised language processes, the frontal diffusion values might have reflected those of the temporal lobe. However, Bernal and Ardila (2009) have recently postulated that the arcuate fasciculus does not directly connect Wernicke’s area in the temporal lobe to the inferior frontal gyrus (or Broca’s area), but instead follows an indirect route via premotor areas. While afferent and efferent connections are not distinguishable using tractography, it is possible that pathways originating from frontal language regions are not as prominent and directionally coherent as those originating from temporal language regions. Thus, any asymmetries in FA that were due to language-related pathways may not constitute a large enough proportion of the frontal lobe sample to be seen as frontal asymmetry in the current study. Indeed, different regions within the prefrontal cortex can give rise to opposing FA asymmetries (Park et al., 2004). Future studies are clearly necessary to explore more functionally specific regions of the frontal cortex, given its involvement in diverse cognitive functions.

4.3. Occipital asymmetries

We did not necessarily expect anatomical asymmetries in the occipital regions, as functional asymmetries are not generally reported here. However, there have been previous reports of similar leftward asymmetries (higher FA in the left) in the optic radiation (Park et al., 2004), and greater white matter volume in the left occipital than the right (Allen, Damasio, Grabowski, Bruss, & Zhang 2003). Although some functional studies have shown a rightward laterality in the occipital areas (e.g. Large, Aldcroft, & Vilis, 2007; Liu et al., 2009), this finding appears to depend on the nature of the stimuli presented (e.g. Han et al., 2002), indicating that the structure-function relationship here may be complex. The left-greater-than-right FA was due to an inverse pattern of perpendicular and parallel diffusion. Again with reference to Schwartz et al.’s (2005) work, the higher parallel diffusion in the left occipital combined with greater perpendicular diffusion in the right might suggest greater axon diameter and/or packing density in the left occipital than the right. Moreover, according to Harsan et al. (2007), greater FA along with less perpendicular diffusion in the left occipital tracts may indicate greater myelin in these axons compared to the right.

4.4. Temporal asymmetries

The FA difference observed between the temporal tracts appears to be purely due to differences in parallel diffusion, since no significant asymmetry was found for perpendicular diffusion. Left temporal regions may have greater directional coherence than the right and perhaps greater axon diameter. Indeed, post-morten
studies have shown asymmetries in cytoarchitecture between temporal regions, specifically in areas relevant to language functions. For instance, Anderson, Southern, and Powers (1999) found thicker myelin in the left relative to the right superior temporal lobe, but reported no differences in axon diameter. Using a slightly different histological approach, Galuske, Scholte, Bratzke, and Singer (2000) found greater spacing of neuronal clusters in the left hemisphere suggesting more functionally distinct subsystems in the language-dominant hemisphere. Consistent with our data, Powell et al. (2006) reported a significant leftward asymmetry in FA values of the arcuate fasciculus, particularly in highly lateralized individuals. Other studies have also reported leftward asymmetries in temporal white matter volume (e.g. Glasser & Rilling, 2008; Pujol et al., 2002). However, it should be noted that in contrast, Park et al. (2004) reported greater FA in the right superior and inferior longitudinal fasciculus in healthy males.

In summary therefore, while a previous histological experiment on rats found no significant interhemispheric differences in axon morphology (Partadiredja et al., 2003), the current study (while not employing a direct measure) found significant differences that likely reflect anatomical differences that underlie the functionally asymmetric processes. These asymmetries are perhaps unique to, expressed to a greater degree, or expressed more consistently, in humans. Nevertheless, Miller’s (1996) hypothesis of a greater number of fast-conducting cortico-cortical connections in the right, relative to the left hemisphere, was not unequivocally supported. Such a scheme may hold however, for a right fronto-parietal network involved in visuospatial or attentional processing.

It should be noted that our subjects were right-handed males. This group was chosen for their more consistent direction and degree of asymmetries. Handedness and sex has some bearing on functional asymmetries (e.g. Allen et al., 2003; Amunts et al., 2007; Ludders et al., 2003; Shaywitz et al., 1995), and will therefore likely have an effect on anatomical asymmetries. These factors will need to be investigated in future studies. Finally, it has been suggested that there is a single dimension of asymmetry (perhaps influenced by a single gene) that underlies functional and anatomical lateralisation (Annett, 1964; Crow, 1999). Certainly the pattern of, particularly parallel, diffusion asymmetries described in the current study is not dissimilar to the cerebral ‘torque’ discussed by Crow (e.g. Crow, 1999). However it has also been argued recently, based on factor analysis of intrinsic fMRI connectivity data, that a single gene cannot explain the multiple lateralisation effects (Liu et al., 2009), a notion subsequently supported by Badzakova-Trajkov, Häberling, Roberts, & Corballis (2010). It might be the case, that cerebral asymmetries in DTI-derived values across large areas of cortex as obtained here might be the sum of a number of competing influences. It is possible that there is a global rightward lateralising influence that results in a greater number of faster conducting, myelinated cortico-cortical axons in the right hemisphere as originally suggested by Miller (1996). Our data from the frontal and parietal lobes is certainly consistent with this view. That we did not see the same pattern across temporal lobes, for example, may be due to a competing influence that specifically or locally left lateralises in language networks. Removal of the arcuate fasciculus, for example, from the analysis might unmask a rightward trend in temporal lobes also. Details such as these will need to be explored in subsequent research. Nevertheless, the different directions of structural asymmetry seen in the current study are consistent with the view that there are multiple lateralising influences.

5. Conclusion

In conclusion, using DTI and probabilistic tractography, we studied white matter asymmetries in healthy individuals. Commonly reported FA values showed significant asymmetries in only the parietal (rightwards) and occipital tracts (leftwards) although there was a trend toward a difference in the temporal. However on examination of parallel and perpendicular diffusion, we observed significant asymmetries in all pathways. Specifically, measures of parallel diffusion showed a rightwards asymmetry in the frontal and parietal lobes, and leftward asymmetry in temporal and occipital. The overall pattern illustrates the complexity of global white matter asymmetries that cannot be detected from FA values alone. However, asymmetries in diffusion were potentially consistent with a variety of functional asymmetries that have been documented to occur in particular lobes, and support the idea that there are multiple lateralising influences contributing to asymmetries in the human brain.

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