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Intrahemispheric white matter asymmetries: the missing link between brain structure and functional lateralization?

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Abstract: Hemispheric asymmetries are a central principle of nervous system architecture and shape the functional organization of most cognitive systems. Structural gray matter asymmetries and callosal interactions have been identified as contributing neural factors but always fell short to constitute a full explanans. Meanwhile, recent advances in *in vivo* white matter tractography have unveiled the asymmetrical organization of many intrahemispheric white matter pathways, which might serve as the missing link to explain the substrate of functional lateralization. By taking into account callosal interactions, gray matter asymmetries and asymmetrical interhemispheric pathways, we opt for a new triadic model that has the potential to explain many observations which cannot be elucidated within the current frameworks of lateralized cognition.

Keywords: arcuate fasciculus; corpus callosum; DTI; laterality; lateralization; superior longitudinal fasciculus; uncinate fasciculus; white matter.

Introduction: functional hemispheric asymmetries

The term functional hemispheric asymmetry (FHA) refers to functional differences between the left and the right side of the brain as evident in behavioral performance or brain activation. FHAs are an important principle of functional nervous system organization not only in humans (as initially thought) but also in other bilateral

species (e.g. Vallortigara et al., 2001; Pascual et al., 2004; Vallortigara, 2006; Rogers, 2008; Frasnelli et al., 2012; Ocklenburg et al., 2013c; Ströckens et al., 2013; Sarasa et al., 2014). In humans, FHAs have been reported in several cognitive domains, ranging from motor control of the hands (Ziemann and Hallett, 2001; McManus et al., 2013; Ocklenburg et al., 2013a; Guadalupe et al., 2014) to emotion (Lindell, 2013; Grimshaw and Carmel, 2014), language (Van der Haegen et al., 2013; Hirnstein et al., 2014; Ocklenburg et al., 2014a; Westerhausen et al., 2014), spatial attention (Nicholls et al., 2010; Thomas et al., 2014), face processing (Meng et al., 2012; Dundas et al., 2013), sense of body ownership (Ocklenburg et al., 2011) and memory (Habib et al., 2003; Babiloni et al., 2006). Hemispheric asymmetries are usually relative, e.g. if one hemisphere is dominant for one specific cognitive function; this does not imply that the neuronal network involved in this function does not involve areas in the other hemisphere. This principle can be illustrated in the language system. In most individuals, the left hemisphere shows greater brain activation during language production and perception. However, the right hemisphere shows strong involvement in certain aspects of these processes, including prosodic, affective and paralinguistic aspects of language production (Ross, 1993; Mitchell and Crow, 2005; Lindell, 2006).

In addition to their substantial relevance for functional organization of the healthy brain, FHAs are altered in a number of neurodevelopmental and psychiatric disorders. A higher incidence of atypical asymmetries (e.g. left- instead of right-handedness or right- instead of left-hemispheric language dominance) has been reported in autism (Lindell and Hudry, 2013), dyslexia (Bishop, 2013), schizophrenia (Sommer et al., 2001; Ocklenburg et al., 2013d; Hirnstein and Hugdahl, 2014) and many others. Thus, understanding the neurobiological underpinnings of FHAs would not only substantially contribute to our knowledge of the functional architecture of the vertebrate brain, but might also give important impulses for research on the etiology of these disorders. Unfortunately, the ontogenetic determinants of FHAs are still largely unknown, but there are at least some leads. For example, several studies have identified the structural properties of

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different brain regions and tracts as factors that may influence functional lateralization (Wada, 2009). In principle, there are two major research approaches which we elucidate in the following two sections.

Gray matter asymmetries as determinants of FHAs

On the one hand, structural gray matter asymmetries (SGMAs), e.g. left-right differences in volume, shape, cortical thickness, surface or microstructural features of distinct brain regions (Amunts, 2010), have been suggested to underlie FHAs (Hervé et al., 2013). Basically, this idea is following the simple logic that stronger SGMAs lead to stronger FHAs, assuming that an increase in one of the structural parameters enhances functional efficacy. For example, if a language-relevant brain region shows stronger SGMAs, one would assume stronger language FHAs due to a relative increase of neuronal tissue in the dominant hemisphere (see Figure 1A).

SGMAs have for example been observed in Heschl's gyrus (Pfeifer, 1920; Marie et al., 2015). The most prominent SGMA in the human cortex is probably that of the planum temporale, a leftward asymmetric intrasylvian area on the planar surface of the superior temporal sulcus that has been related to language perception (Galaburda et al., 1990; Steinmetz et al. 1991; Chance, 2014). However, its relation to language lateralization is complicated. For example, Dos Santos Sequeira et al. (2006) investigated the relation of the leftward structural asymmetry of the planum temporale with functional language lateralization, as reflected by the right ear advantage in the classic dichotic listening task. They found a positive correlation between structural asymmetry of the planum temporale and functional lateralization in the dichotic listening task in right-handed males, indicating that in this group, stronger SGMAs corresponded with stronger FHAs. However, no such relation was found in male left-handers or female left- and right-handers.

Other more recent studies also indicated that while SGMAs clearly exist, their relation to FHAs is subtly at least. Greve et al. (2013) compared gray matter volume asymmetries in participants that had previously been determined to be left- or right-dominant for language using fMRI. The planum temporale, pars opercularis, Heschl's gyrus and the insula showed significant left volume lateralization in both groups of participants. Interestingly, a significant difference between the two groups was only observed for the insula, with a larger volume being

observed in left-dominant compared to right-dominant participants. Moreover, Greve et al. (2013) correlated the individual extent of gray matter volume asymmetries with different behavioral and fMRI measures of functional language lateralization. While left-right asymmetry of insula volume correlated with functional asymmetry in the dichotic listening task and brain activation asymmetry during word generation in the fMRI, asymmetries in the other ROIs, including the planum temporale and Broca's area, failed to show a significant relation with functional asymmetries. Similar findings were also reported by Chiarello et al. (2013). Also, an important factor that has to be taken into account when interpreting gray matter asymmetries is that depending on the measure used to determine SGMAs, the anatomical asymmetry can change substantially. Meyer et al. (2014) showed that cortical volume, cortical thickness and cortical surface area demonstrate different lateralization patterns in perisylvian brain regions. Taking all of these results into account, it is thus unlikely that SGMAs are the only structural determinant of functional lateralization.

White matter structure as a determinant of FHAs

The role of the corpus callosum

The other major research approach regarding the structural determinants of FHAs suggests that the structural properties of the corpus callosum, the major commissure in the human brain (Fabri et al., 2014), are of central importance for the existence and extent of FHAs. There is abundant evidence supporting this view (Witelson, 1985; Aboitiz et al., 1992; Hines et al., 1992; Clarke and Zaidel, 1994; Moffat et al., 1998; Westerhausen and Hugdahl, 2008; Nowicka and Tacikowski, 2011; but also see Jäncke and Steinmetz, 1994). Most callosal axons rely on glutamate, an excitatory neurotransmitter, but due to the presence of inhibitory interneurons, callosal information transfer can also be inhibitory (van der Knaap and van der Ham, 2011). This has led different authors to propose both excitatory and inhibitory models for the relation of corpus callosum structure and functional lateralization.

For example, assuming excitatory information transfer, Ringo et al. (1994) proposed that a smaller corpus callosum would lead to stronger FHAs, due to the assumption that time-sensitive processes are more likely to be performed by faster intrahemispheric circuits than the

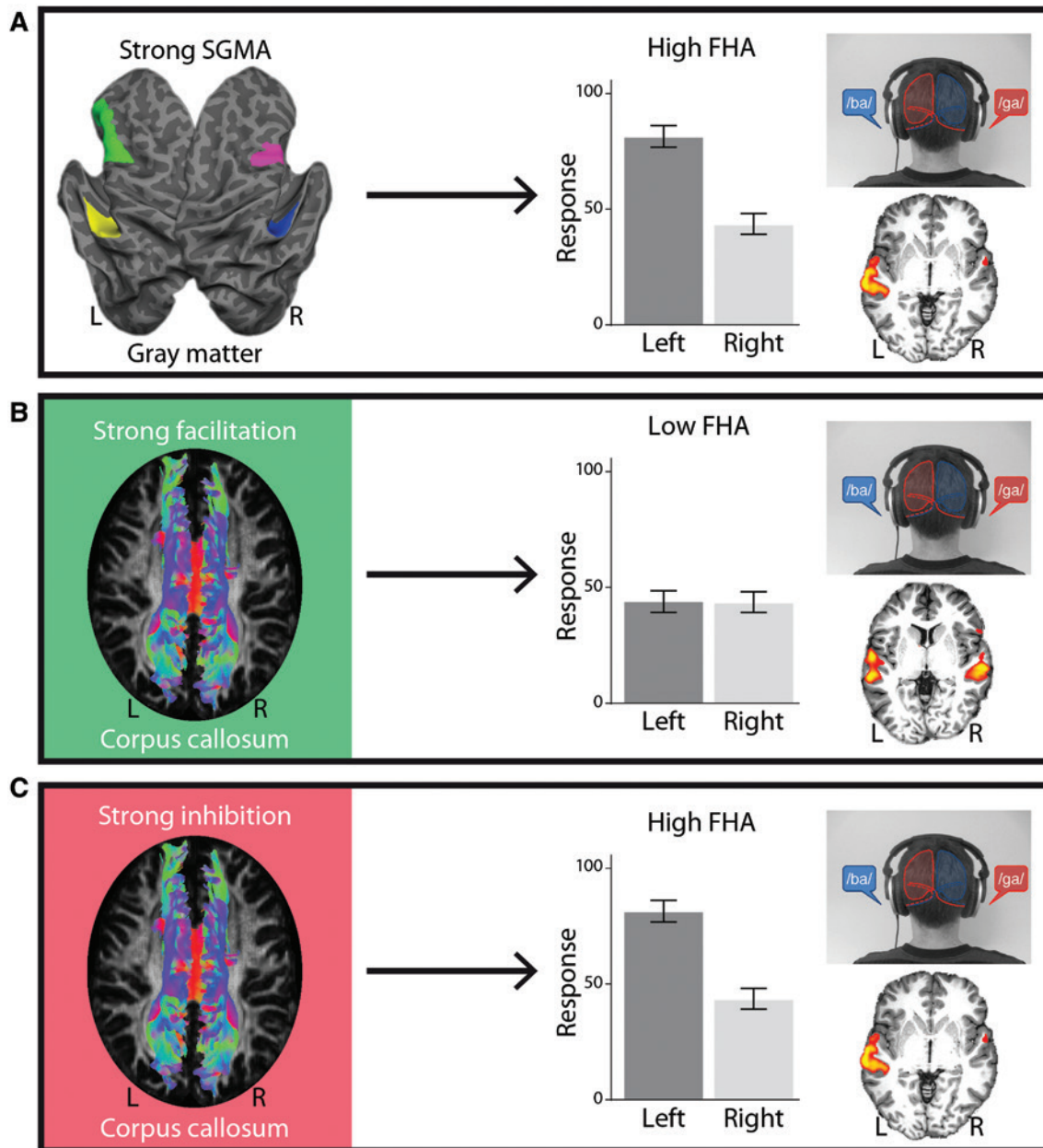


Figure 1: SGMA and the function of corpus callosum as determinants for lateralized cognition in humans. (A) SGMA leads to higher FHA, e.g. a language-relevant brain region such as Broca's area (green) or planum temporale (yellow) has more neuronal tissue and therefore higher efficacy in the left hemisphere than in the corresponding location in the right hemisphere (magenta and dark blue areas). Higher FHA is reflected in asymmetric responses during behavioral tasks (e.g. dichotic listening task, top right) or in asymmetric BOLD responses in brain areas relevant for language perception (bottom right). (B) Ringo et al. (1994) proposed that a bigger corpus callosum is associated with faster and more interhemispheric exchange of information (strong facilitation as colored in green) and less functional specialization. This would be reflected in a more symmetric response in behavioral tasks or activity of task relevant brain regions. In contrast, a smaller corpus callosum would hinder fast time-sensitive processes across the hemispheres and therefore will lead to independence and thus functional specialization of each hemisphere. (C) However, an alternative model assumes that stronger callosal interactions, especially when the dominant left hemisphere strongly inhibits (as colored in red) the subdominant right counterpart, leads to functional specialization of one hemisphere. Higher FHA would be reflected in asymmetric responses in behavioral tasks or activity of task relevant brain regions. If the inhibition is absent, less functional specialization is established, respectively. Abbreviations: L, left; R, right.

slower interhemispheric circuits across the corpus callosum (see Figure 1B). This model was for example supported by a study by Yazgan et al. (1995), who found that

the midsagittal area of the corpus callosum correlated negatively with the extent of behavioral lateralization in the dichotic listening task, i.e. the right ear advantage in

this task became smaller with greater corpus callosum size. Interestingly, this model also implies that brain size might be a relevant factor for the ontogenesis of FHAs, as this variable has been shown to modulate callosal function (Steinmetz et al., 1995; Hänggi et al., 2014; Luders et al., 2014).

In contrast to the approach by Ringo et al. (1994), inhibitory models of corpus callosum structure and FHAs assume that the dominant hemisphere strongly inhibits the subdominant one via the corpus callosum. Thus, a smaller corpus callosum would lead to less pronounced FHAs (Cook, 1984; Bloom and Hynd, 2005; see Figure 1C). This idea was for example supported by the work of Josse et al. (2008), who investigated the relation of the midsagittal surface area of the corpus callosum with language-related brain activation asymmetries measured with fMRI. They found that participants with a larger corpus callosum showed stronger left-hemispheric language dominance in inferior frontal and posterior temporal brain regions.

While the two models are seemingly contradictory, two comprehensive reviews on the subject (Bloom and Hynd, 2005; van der Knaap and van der Ham, 2011) concluded that the corpus callosum likely serves both excitatory and inhibitory influences on the contralateral hemisphere. This could for example be attained by functional differences in specific callosal fiber types, subregions, targeted interneurons or differential activity in intrahemispheric functional networks. Taking this perspective into account, using gross callosal midsagittal size as a marker for callosal functioning might not be an optimal choice in studies on structural determinants of FHAs. Instead, linking the structural properties of functionally divergent subregions of the corpus callosum might yield greater insights into the structural determinants of FHAs. For example, Hofer and Frahm (2006) used DTI-based white matter tractography to distinguish five vertical segments of the corpus callosum containing fibers projecting into functionally different cortical areas. In regard to an asymmetric cognitive phenomenon, the anatomical segmentation of the corpus callosum seems to be important as shown in a study by Gootjes et al. (2006). In healthy elderly participants, these authors found significant negative correlations between the right ear advantage in the dichotic listening task and the area of the most anterior and the most posterior of five callosal segments, but not with the area of the three intermediate subsegments. While much remains to be investigated regarding the role of subsegments of the corpus callosum for FHAs, we can conclude that the corpus callosum clearly is an important factor for the ontogenesis of FHAs. This conclusion is also supported by the recent work in non-human primates (Hopkins et al., 2015).

However, from a comparative perspective, there is one major problem in assuming that the corpus callosum is the main determinant of FHAs. While only Eutherian (placental) mammals have a Corpus callosum (Suárez et al., 2014), recent studies indicate that FHAs are also present in marsupials, e.g. in the red-necked wallaby (Giljov et al., 2012). Moreover, a large number of birds, reptiles, amphibians, fishes and even invertebrates show FHAs (Bisazza et al., 1998; Frasnelli, 2013; Rogers et al., 2013; Ströckens et al., 2013; Manns and Ströckens, 2014), indicating that FHAs can develop in the absence of the corpus callosum, making it likely that other structural properties of the brain are also important for the emergence of FHAs, such as the structure of the commissura anterior or intrahemispheric pathways.

Intrahemispheric white matter asymmetries: the missing link?

From the preceding section, it can be concluded that up to now SGMAs and callosal interactions have been identified as important neural factors contributing to functional lateralization. However, it is also clear that these two factors do not offer the complete picture. The findings of different studies are sometimes contradictory, effects might be limited to certain subsamples of the overall sample and effect sizes are typically small. From our perspective, a major problem with many studies is the fact that they assess structural properties of either the corpus callosum or a single gray matter structure and relate them to function. As no brain structure functions in isolation and no cognitive function is determined by a single brain area, this approach only yields an incomplete picture of structure-function relationships and always fell short to constitute a full explanans. Recent advances in whole brain connectivity analysis meanwhile deliver an answer why: Both on the functional and on the structural level, intrahemispheric brain connections are organized in a fundamentally asymmetrical fashion. This insight started with a study by Iturria-Medina et al. (2011), who used DTI and graph theory to determine the structural network properties of the left and right hemisphere. They observed that the right hemisphere had greater intrahemispheric global efficiency and more interhemispheric interconnections than the left hemisphere. In contrast, the left hemisphere showed more intrahemispheric local connections, particularly for brain areas related to language and fine motor coordination. These findings were supported by a recent study by Caeyenberghs and Leemans (2014), who showed that nodal efficiency in left-hemispheric networks

is increased in brain areas involved in language and motor coordination, while right-hemispheric networks showed increased nodal efficiency in brain areas related to visuospatial attention and memory. Importantly, using fMRI resting state connectivity analysis, Gotts et al. (2013) showed that these asymmetries in structural connectivity are reflected by two distinct forms of lateralization in functional connectivity: the regions in the left hemisphere showed more intrahemispheric connections, whereas regions in the right hemisphere proved to interact more strongly in a bilateral fashion. Notably, these two different connectivity patterns were related to behavioral measure of left- and right-dominant cognitive functions. While the individual magnitude of left-hemispheric lateralization predicted verbal ability, right-hemispheric lateralization predicted visuospatial ability, proving that lateralization of functional networks is relevant for lateralized cognition. Apart from whole-hemisphere connectivity differences, recent *in vivo* white matter tractography studies have shown structural left-right asymmetries for a number of individual intrahemispheric white matter pathways (see the next sections for detailed descriptions). They thus connect critical functional and structural nodes within the two hemispheres in a lateralized manner.

We propose that these intrahemispheric white matter asymmetries are the missing link that connects gray matter asymmetries on the one side and callosal function on the other. Only by integrating those three structural determinants, the emergence of FHAs can be explained. Indeed, several studies that demonstrated asymmetries of intrahemispheric white matter pathways can explain lesion results that otherwise are difficult to understand. For example, it is impossible to understand left-lateralized language function without taking intrahemispheric connectivity into account. This principle is illustrated in patients with conduction aphasia, an acquired disorder of the language system, characterized by relatively fluent, but often paraphasic speech and difficulties with speech repetition. In contrast, auditory comprehension remains intact (Ardila, 2010). While initially thought to be the result of a disconnection between Broca's and Wernicke's area, the cause of conduction aphasia remains a matter of debate (Bernal and Ardila, 2009). Interestingly, however, almost all patients seem to have left-hemispheric lesions. For example, in an analysis of 20 acute cases of conduction aphasia by Bartha and Benke (2003), all 20 patients had experienced left-hemispheric lesions. Importantly, conduction aphasia massively impacts behavioral FHAs. In a dichotic listening study with two patients with conduction aphasia, Damasio and Damasio (1980) showed that both patients did not report a right-ear stimulus even

a single time, while for all 110 trials the left-ear stimulus was reported. On a subjective level, patients reported that while they heard words on the right ear, they were unable to distinguish the sounds from one another. Obviously, such results would not be explainable with only gray matter asymmetries and structural properties of the corpus callosum. To further exemplify the importance of intrahemispheric white matter asymmetries for lateralized cognition, we will review exemplary evidence for the functional relevance of structural asymmetries in different intrahemispheric white matter tracts.

The role of the arcuate fasciculus for functional language lateralization

The most widely investigated white matter pathway in regard to structural white matter asymmetries is probably the arcuate fasciculus. The arcuate fasciculus is a lateral association tract that was initially thought to only connect Broca's area to Wernicke's area, but is now understood to be part of a larger tract, the superior longitudinal fasciculus (SLF; Ardila, 2010). It bidirectionally connects the perisylvian regions of the parietal and temporal cortex to the frontal lobe (Catani and Thiebaut de Schotten, 2008; see Figure 2).

Functionally, the left arcuate fasciculus has been found to support a multitude of functions in the language system (for review, see Friederici, 2015; Friederici and Gierhan, 2013), as well as being relevant for the ability to perform voluntary skilled movements (Heilman and Watson, 2008). The right arcuate fasciculus, in contrast, has been shown to be relevant for visuospatial processing (Doricchi et al., 2008) and prosodic aspects of language processing (Glasser and Rilling, 2008). Structural left-right asymmetries in the arcuate fasciculus have been reported for several different micro- and macrostructural measures. The first neuroimaging study to report a left-right asymmetry of the arcuate fasciculus was conducted by Büchel et al. (2004), who used a voxel-based statistical analysis of DTI data obtained from two groups of healthy adult volunteers. In both independently analyzed groups, Büchel et al. (2004) found significantly greater fractional anisotropy (FA) of the left compared to the right arcuate fasciculus. While the exact functional significance of FA remains a matter of debate, many authors assume it to be a measure of microstructural integrity (Alexander et al., 2007); thus these results implicate that the left arcuate fasciculus transports neuronal information more efficiently than the right. After the initial study by Büchel et al. (2004), several other authors independently replicated

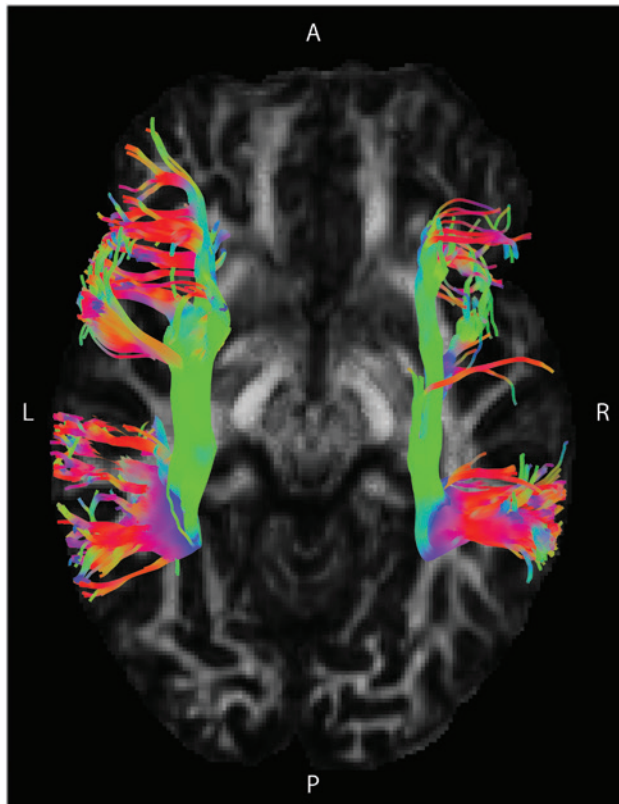


Figure 2: Axial view of the left and right human arcuate fasciculus. Unless otherwise stated, in all other figures the white matter fibers are tracked by *in vivo* spherical deconvolution DTI fiber tractography and are overlaid onto the fractional anisotropy map of an representative individual; the colors represent fiber orientations in different directions: right-left (red), anterior-posterior (green) and superior-inferior (blue). Abbreviations: L, left; R, right; P, posterior; A, anterior.

the finding that the arcuate fasciculus (or at least parts of it) shows greater FA in the left than in the right hemisphere (e.g. Powell et al., 2006; Catani et al., 2007, 2010; Rodrigo et al., 2007; Upadhyay et al. 2008; Lebel and Beaulieu, 2009; O'Donnell et al., 2009; Choi et al., 2010; Takao et al., 2011, 2013; Häberling et al. 2013; Ocklenburg et al., 2013b; James et al. 2015; but see Park et al., 2004).

In addition to FA asymmetries, several authors reported left-right differences in the arcuate fasciculus using macrostructural measures. For example, Nucifora et al. (2005) found that the left arcuate fasciculus showed a greater relative fiber density than its right-hemispheric counterpart in a sample of 27 healthy adult volunteers. This finding was subsequently replicated by Vernooij et al. (2007). Moreover, the tract volume of the left arcuate fasciculus has been shown to be larger than that of the right (Powell et al., 2006; Schlaug et al., 2009; Propper et al., 2010; Ocklenburg et al., 2014b; James

et al., 2015; Sreedharan et al., 2015) and a leftward asymmetry has been shown for tract length as well (Propper et al., 2010).

Left-right asymmetries of the arcuate fasciculus have an impact on cognitive functioning (Catani et al., 2007; Lebel and Beaulieu, 2009) and importantly, they have been shown to affect FHAs. In a combined fMRI and DTI study, Powell et al. (2006) tested 10 healthy adult right-handers with three language paradigms in the fMRI and performed probabilistic tractography on the DTI data. They found that both FA and tract volumes were significantly greater in the left compared to those in the right hemisphere. While no correlation between tract volume asymmetry and fMRI activation asymmetry was observed, FA lateralization correlated with fMRI activation asymmetries during verb generation in the frontal lobes and during reading comprehension in the temporal lobes. In both cases, subjects with more FA lateralization also showed greater functional activation asymmetries in the fMRI. Subsequently, Vernooij et al. (2007) showed that asymmetries in the relative fiber density of the arcuate fasciculus were also related to FHAs. In a sample of 20 healthy volunteers, they showed that the arcuate fasciculus has a greater relative fiber density in the left compared to the right hemisphere. In right-handers, but not in left-handers, this structural asymmetry was positively correlated to brain activation asymmetries during a verb generation task in the fMRI. These findings implicate that handedness might be an important variable to assess, in the context of research on asymmetries of the arcuate fasciculus, a notion that is also supported by a more recent study by Propper et al. (2010). These authors found that the arcuate fasciculus showed a significantly greater volume and length in the left compared to those in the right hemisphere. They reported that the extent of asymmetry in arcuate fasciculus volume correlated significantly with fMRI activation asymmetries during an antonym generation task in consistent left-handers. No correlations were observed for activation asymmetries in Broca's area or in right-handed subjects. More recently, Ocklenburg et al. (2013b) used tract-based spatial statistics (TBSS) in a sample of 29 healthy adult volunteers to detect structural white matter asymmetries. Several clusters showing significant FA left-greater-than-right asymmetries were identified in the arcuate fasciculus. These microstructural asymmetries showed significant positive correlations to frontal and temporal brain activation asymmetries during silent word generation in the fMRI, indicating that subjects with stronger structural asymmetries also showed stronger FHAs. Similar results were

obtained by James et al. (2015) as well. These authors also observed a positive correlation between a laterality index for structural asymmetries in the arcuate fasciculus and functional activation asymmetries during language fMRI in a mostly right-handed sample.

Interestingly, a relation of structural arcuate fasciculus asymmetries and functional language lateralization has not only been observed in adults, but also in preadolescent children. Sreedharan et al. (2015) tested children between 8 and 12 years using two fMRI language paradigms and assessed FA and fiber volume of the left and right arcuate fasciculus using DTI. They found that the average laterality index for the two fMRI tasks showed a significant positive correlation with a laterality index calculated for fiber volume asymmetries of the left and right arcuate fasciculus, indicating that children with a stronger volume asymmetry in the arcuate fasciculus also showed stronger brain activation asymmetries during language tasks in the fMRI. This effect was driven by both a positive correlation between the fMRI laterality index and the volume of the left arcuate fasciculus and a negative correlation between the fMRI laterality index and the volume of the right arcuate fasciculus. Unfortunately, Sreedharan et al. (2015) did not report any correlations between functional language lateralization and FA asymmetries.

A relation of FHAs and arcuate fasciculus structure was further supported by a patient study by Matsumoto et al. (2008). These authors performed DTI-based tractography of the arcuate fasciculus in 24 epileptic patients in which the language-dominant hemisphere had been determined using the Wada test. For analysis, Matsumoto et al. (2008) divided the arcuate fasciculus into two segments, one terminating in the parietal lobe and the other in the temporal lobe. They found that the segment of the arcuate fasciculus termination in the temporal lobe showed a greater volume in the language-dominant hemisphere, while no relations to FHAs were found for the other segment.

Taken together, there is substantial evidence for a left lateralization of the arcuate fasciculus on both the micro- and macrostructural level. Several studies investigating the relation of these leftward structural asymmetries to FHAs found positive correlations, although the occurrence of FHAs seems to be somewhat task dependent and is modulated by handedness. While clearly more research in larger samples is needed to clarify the role of handedness, all studies so far support the idea that leftward asymmetry of the arcuate fasciculus might be one of the factors underlying leftward functional language lateralization.

The uncinete fasciculus

Another white matter tract that has been shown to exhibit structural left-right asymmetries is the uncinete fasciculus (see Figure 3). The uncinete fasciculus is a lateral association tract that connects the anterior temporal lobe with the orbitofrontal cortex (Thomas et al., 2015). The functional role of the uncinete fasciculus is less well understood than that of the arcuate fasciculus, but in a recent review article, Von Der Heide et al. (2013) listed three putative functions. These include linguistic functions, in particular naming (Papagno, 2011), social-emotional functions (Zuurbier et al., 2013) and memory (Schaeffer et al., 2014).

While many authors agree that the uncinete fasciculus shows structural asymmetries, the direction of these asymmetries is much more controversial than for the arcuate fasciculus. For example, most authors reported that (comparable to what has been observed for the arcuate fasciculus) the left uncinete fasciculus shows higher FA than its right-hemispheric counterpart (Kubicki et al., 2002; Hasan et al., 2009, 2010; Rocca et al., 2009; Danielian et al., 2010; Jahanshad et al., 2010; Ocklenburg et al., 2013b). However, there are several studies that found FA values of the right uncinete fasciculus to be higher than

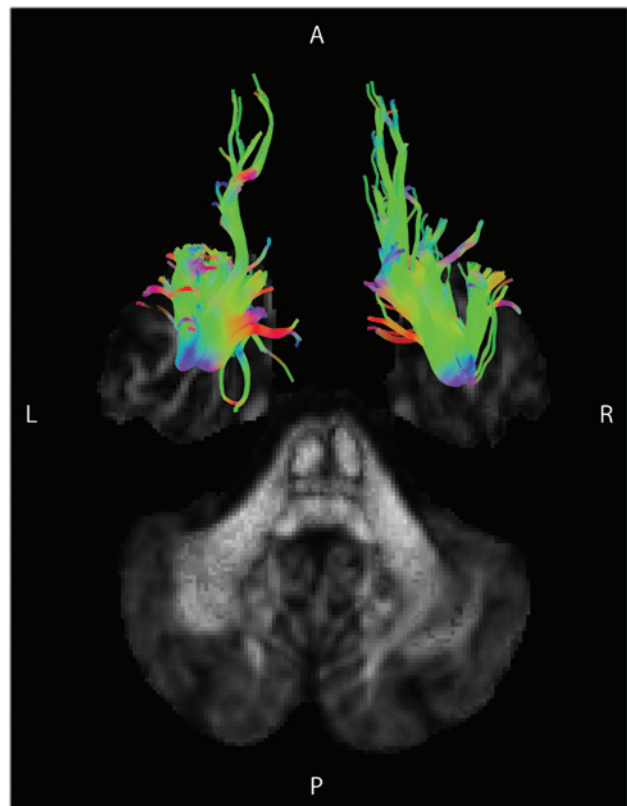


Figure 3: Axial view of the left and right human uncinete fasciculus.

those of the left one (Park et al., 2004; Yasmin et al., 2009; Takao et al., 2011, 2013; Madsen et al., 2012; DeRosse et al., 2015), whereas some studies did not find any differences in FA between the right and the left uncinate fasciculus (Malykhin et al., 2008; Hernando et al., 2015).

The cause of this high interstudy variability is not clear. Besides methodological differences between different studies, sample selection surely plays a role. Similar to what has been found for the arcuate fasciculus, subjects handedness seems to affect uncinate fasciculus asymmetries, as James et al. (2015) reported higher FA in the left uncinate fasciculus in right-handers, but no asymmetries in left-handed or ambidextrous subjects. Moreover, subjects' sex could have an impact, as Kitamura et al. (2011) reported a sex difference in FA of the right uncinate fasciculus, with female subjects showing higher average FA values. Also, different segments of the uncinate fasciculus possibly show differences in structural asymmetry. Rodrigo et al. (2007) reported a significant left-greater-than-right FA asymmetry for the subinsular parts of the uncinated fasciculus and a significant right-greater-than-left FA asymmetry in the extrainsular part of the uncinate fasciculus. Clearly, more large-scale studies systematically varying sample characteristics such as handedness and gender as well as meta-analytical integrations are needed to clarify this issue. For uncinate fasciculus tract volume, the results are similarly ambiguous as for FA. While some authors reported a leftward volume asymmetry of the uncinate fasciculus (Wakana et al., 2007; Ocklenburg et al., 2014b; James et al., 2015), others found the reverse pattern (Malykhin et al., 2008; Takao et al., 2013).

Despite the ambiguity of the structural results, some authors found associations between uncinate fasciculus asymmetries and brain function. For example, Madsen et al. (2012) reported that the cortisol awakening response, a measure that has been linked to neuroticism and limbic system functioning, was positively correlated with FA asymmetries in the uncinate fasciculus. Evidence for a relation of uncinate fasciculus asymmetries and FHAs comes from a TBSS study by Ocklenburg et al. (2013b), who, comparably to the arcuate fasciculus, found several clusters showing significant left-greater-than-right FA asymmetries in the uncinate fasciculus. One of these microstructural asymmetries showed a significant positive correlation with temporal brain activation asymmetries during passive listening to verbal stimuli in the fMRI, indicating that subjects with stronger structural uncinate fasciculus asymmetries also showed stronger FHAs. More recently, Ocklenburg et al. (2014b) also found that the volume of the right uncinate fasciculus was

positively correlated with functional language lateralization measured with the dichotic listening task.

Taken together, it is relatively undisputed that the uncinate fasciculus shows asymmetries on both the micro- and the macrostructural level. Curiously, however, it is not clear whether it is left- or right-lateralized, as several studies support both views. While this issue remains to be clarified by future studies, there is at least some evidence that stronger structural uncinate fasciculus asymmetries might lead to stronger language FHAs. However, more research is needed before any final conclusions can be drawn on this matter.

White matter and attention

Most research on white matter asymmetries concentrated on the arcuate fasciculus and consequently functional asymmetries in language processing for which most individuals show a left-hemispheric dominance. There is, however, growing evidence for a possible involvement of rightward white matter asymmetries for FHAs. For example, Barrick et al. (2007) performed whole brain tractography in 30 healthy adult right-handers and identified pathway connecting the posterior temporal lobe to the superior parietal lobule that showed a right-greater-than-left asymmetry. Barrick et al. (2007) named this pathway, which had not been described previously by other authors, the superior parietal lobule pathway. They suggested that it may have a functional association with auditory spatial attention and spatial working memory, both of which have been shown to show rightward FHAs (Griffiths et al., 1998; Nagel et al., 2013). Unfortunately, Barrick et al. (2007) did not test this assumption experimentally, leaving it to future fMRI/DTI studies to further investigate the relation of the superior parietal lobule pathway structure to rightward FHAs.

However, more recently, direct evidence for a link between rightward white matter asymmetries and rightward FHAs was provided by a DTI study by Thiebaut de Schotten et al. (2011). These authors performed tractography of the three parieto-frontal branches of the SLF, the dorsal SLF I, the middle SLF II and the ventral SLF III (see Figure 4) in 20 healthy adults.

They found that while the tract volume of SLF I did not show any asymmetry, the tract volume of the SLF II showed a non-significant trend towards rightward lateralization. Moreover, there was a significant right-larger-than-left tract volume asymmetry of the SLF III. Thiebaut de Schotten et al. (2011) then assessed FHAs in visuospatial using the line bisection test, a simple behavioral

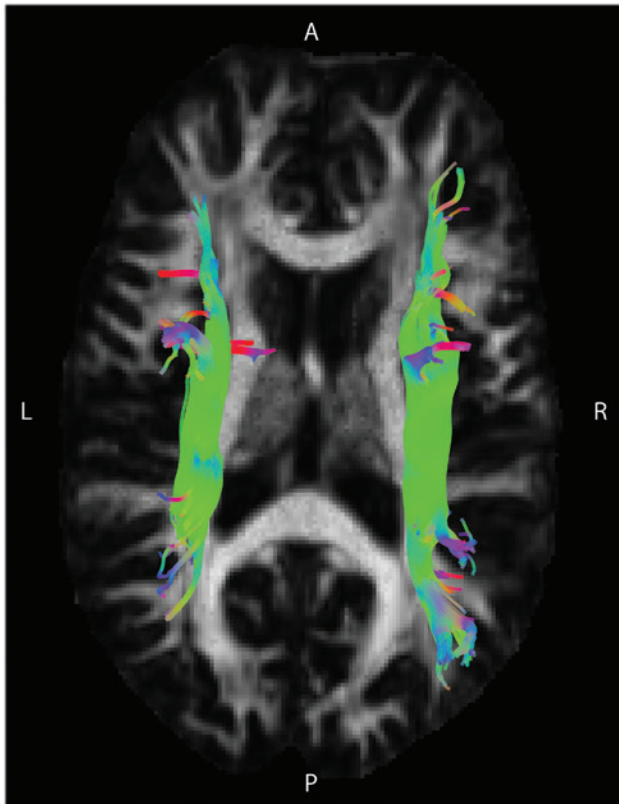


Figure 4: Axial view of the left and right human SLF. For a better illustration, we only show SLF II and III, which are merged in this figure.

task in which subjects are asked to mark the middle of a number of lines of varying length (Beste et al., 2006). Comparable to previous studies, the subjects in the study by Thiebaut de Schotten et al. (2011) showed a small leftward deviation from the true middle of the lines, an effect that has been named ‘pseudoneglect’ and is thought of as a behavioral marker of right-hemispheric dominance for spatial attention. Overall, larger right SLF II volumes were associated with a greater pseudoneglect in the line bisection test, indicating stronger FHAs in visuospatial attention. Interestingly, there were three subjects that showed a rightward instead of the typical leftward deviation in the line bisection test. All three of these subjects also showed atypical structural lateralization of the SLF II, that is a left-greater-than-right volume of the SLF II. Thiebaut de Schotten et al. (2011) then tested the hypothesis that rightward FHAs in visuospatial attention might be the result of speed differences of visuospatial processing between the two hemispheres along the SLF II by testing their subjects with the Posner (1980) paradigm, a simple visual attention task. They found that larger right-hemispheric SLF II volumes were associated with faster

stimulus detection in the left hemifield. Moreover, faster stimulus detection in the left hemifield was also related to a larger pseudoneglect in the line bisection test. Based on these findings, Thiebaut de Schotten et al. (2011) concluded that white matter asymmetries in parieto-frontal connections predict the degree of FHAs in visuospatial attention.

More evidence for a role of white matter structure for visuospatial attention comes from a DTI study in alcoholic patients and healthy controls by Schulte et al. (2010). The authors found that alcoholic patients showed reduced FA in parts of the corpus callosum, particularly those that connect the prefrontal and frontal cortices. Moreover, patients had higher FA in the right compared to the left posterior cingulum, an effect that was not found in healthy controls. In addition to these structural white matter differences, the two groups also behavioral performance differences in a simple lateralized reaction time task, when stimuli were presented bilaterally or unilaterally to the two visual hemifields. Healthy controls showed a greater degree of bilateral processing advantage with the left hand, but less unilateral processing advantage with the right hand, while in patients the bilateral processing advantage when responding with the left hand was reduced and the unilateral processing advantage when responding with the right hand was enhanced. Schulte et al. (2010) concluded that their findings show that intra- and interhemispheric pathways mediate visuomotor integration in an asymmetrical fashion and that white matter degradation in alcoholism therefore modulates hemispheric asymmetry.

Additional evidence for a relation of white matter asymmetries and attention was provided by Yin et al. (2013), who used TBSS to investigate white matter asymmetries and related them to performance in the attention network test. They observed leftward FA asymmetries in the cingulum, corticospinal tract, inferior corona radiata and the cerebral peduncle and rightward FA asymmetry in the internal capsule, SLF and superior corona radiata. While there was no relation between white matter asymmetries and the alerting and orienting subcomponents of behavioral performance in the attention network test, there was a significant positive correlation between the leftward asymmetry of the inferior corona radiata (see Figure 5) and the executive control subcomponent of behavioral performance in the attention network test.

Clearly, more research linking different behavioral and brain activation markers of visuospatial attention and other right-hemispheric FHAs to white matter asymmetries is needed. However, existing research supports the notion that similar to what has been observed for

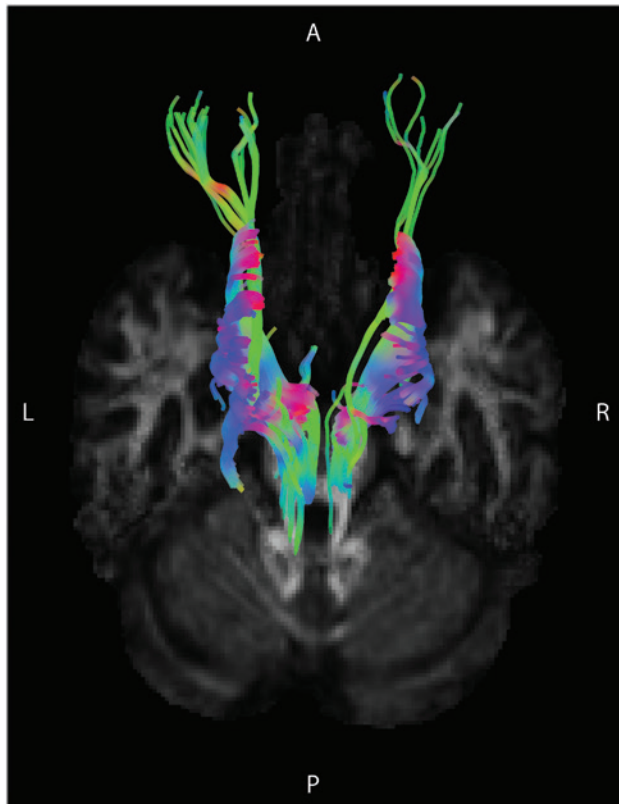


Figure 5: Axial view of the left and right human corona radiata.

language lateralization, right-hemispheric FHAs are also modulated by white matter structure and asymmetries.

Other white matter asymmetries

In addition to the white matter asymmetries described in the previous section, many authors reported evidence for structural asymmetries in other white matter pathways. Just to give a few examples: in addition to FA asymmetries in the arcuate and uncinate fasciculus, Takao et al. (2011) reported the leftward FA asymmetry of the posterior limb of the internal capsule, the cingulum and in the cerebellum, and the rightward FA asymmetry was seen in frontal white matter, the posterior corona radiata and the posterior corpus callosum. Hasan et al. (2010) reported a left-larger-than-right FA asymmetry of the corticospinal tract, while Madsen et al. (2012) reported a left-larger-than-right FA asymmetry in the cingulum. A leftward FA asymmetry of the cingulum also was reported by Park et al. (2004), who found additional leftward FA asymmetries in the optic radiation, the superior cerebellar peduncle, the splenium of the corpus callosum and medial prefrontal white matter. Rightward FA asymmetries were observed in

the anterior prefrontal white matter, the inferior longitudinal fasciculus, the SLF, the anterior limb and posterior limb of the internal capsule and the superior prefrontal white matter. However, the functional relevance of most of these white matter asymmetries is not clear at present and should be investigated by future studies.

Integrating intrahemispheric white matter asymmetries

Taken together, there is substantial evidence that several major intrahemispheric pathways in the human brain are organized asymmetrically. Moreover, recent research suggests that such intrahemispheric white matter asymmetries are a key determinant for the FHAs in the language and attention system. These findings provide us with a strong suggestion of why many previous attempts to explain individual FHAs from brain structure largely failed: a key component was missing. Only using the degree and direction of gray matter asymmetries or structural properties of the corpus callosum to predict FHAs yields an incomplete picture that does not take the complex networks underlying many cognitive functions into account. Thus, we propose that the structural determinants of FHAs can only be understood if system-specific gray matter and intrahemispheric white matter asymmetries as well as properties of the corpus callosum are integrated in a triadic model (see Figure 6). In principle, it could be assumed that for gray matter and intrahemispheric white matter asymmetries, larger regions and thicker or more myelinated white matter tracts lead to stronger FHAs. The relation is less straightforward for the corpus callosum, as exemplified in the section ‘The role of the corpus callosum’. Here, relevant subsegments of the corpus callosum for a specific FHA need to be identified, and based on previous research function-specific inhibitory and/or excitatory properties of these subsegments should be taken into account. Taking these ideas at a next level, we further would integrate, in addition to the specific gray matter and intrahemispheric white matter asymmetries and properties of the corpus callosum as predictors for FHAs, variables reflecting the interaction between these predictors in multivariate statistical analysis methods. While this is rather speculative, one could at least conceive that there are specific configurations in which one structural predictor has a larger impact FHAs than under other circumstances. For example, in individuals with a very inefficient corpus callosum, intrahemispheric white matter asymmetries might have a greater

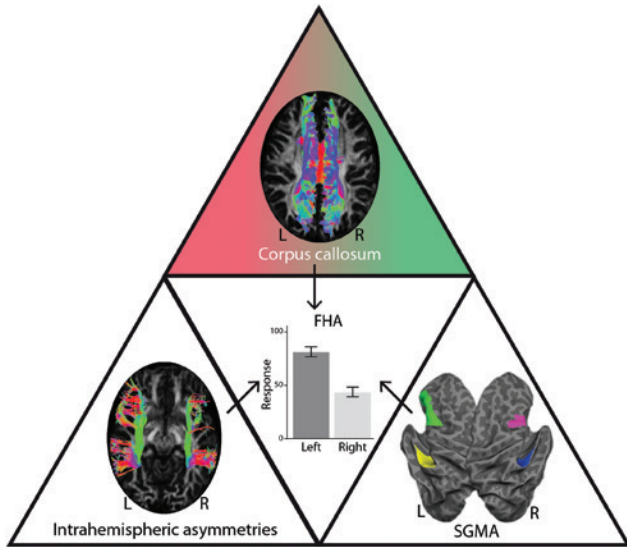


Figure 6: The triadic model: interaction of different anatomical determinants predicting lateralized cognition in humans. We conclude that in addition to SGMA (bottom right) and callosal interaction (top middle), also the asymmetries of intrahemispheric white matter pathways (bottom left) are essential for the understanding of FHA. Importantly, for callosal interaction it is important *which* callosal fibers are relevant for the lateralized functions and whether the interaction is of an inhibitory (red) or a facilitatory (green) fashion. Finally, we assume that each anatomical predictor is independent from each other and will deliver unique contributions to the prediction of FHA.

impact on FHAs than in individuals with a very efficient corpus callosum, since they are forced to rely more on intrahemispheric processing.

One possible criticism of this model is the idea that gray matter and intrahemispheric white matter asymmetries might not be independent of each other. Obviously, differences in gray matter volume are related to intrahemispheric white matter asymmetries since axons derive from somata. However, this relationship is rather weak. For example, Takao et al. (2011) showed that the microstructure of the arcuate fasciculus was positively related to gray matter volume of the planum temporale, but the variance explained by this relationship was <20%. Thus, gray matter asymmetries are in no way one to one translated into intrahemispheric white matter asymmetries. Similarly, gray and white matter asymmetries are only weakly related to measures of callosal structure. Cherbuin et al. (2013) investigated the relation of different structural gray and white matter asymmetries with thickness of the corpus callosum in 348 cognitively healthy older subjects. For gray matter, they found that the direction of asymmetries in the hippocampus, motor cortex and supramarginal cortex was correlated with callosal

thickness, as was the magnitude of asymmetries in the hippocampus, parietal cortex and supramarginal cortex. For white matter, greater asymmetry in the frontal, temporal and parietal lobe was related to lower callosal thickness. While these asymmetries were significant predictors of callosal thickness, the correlations were rather subtle and by no means allowed for a complete explanation of one parameter from one of the others. Thus, intrahemispheric white matter and gray matter asymmetries and corpus callosum structure can be viewed as three largely independent determinants of FHAs.

Outlook

Besides explaining existing findings, a new theoretical approach should primarily stimulate new research. Our triadic model makes several predictions that are easily tested empirically. First of all, it would be important to test the model for different cognitive systems that have been found to be lateralized (e.g. language, emotion, face perception, visuospatial processing) by relating behavioral and brain activity measures of FHAs in these domains to brain structure. Here, asymmetries in macro- and microstructural properties of functionally relevant gray matter areas and white matter tracts, as well as macro- and microstructural properties of functionally relevant subsegments of the corpus callosum could be tested for unique contributions in predicting FHAs. In this regard, it would also be interesting to investigate what the specific role of intrahemispheric white matter asymmetries for the impact of excitatory and inhibitory callosal information transfer on functional lateralization is. In relation to pathological brain development and brain lesions, it would be interesting to investigate to what extent FHAs in split-brain patients and callosal agenetics are driven by intrahemispheric white matter asymmetries. Since these patients lack a corpus callosum, intrahemispheric white matter asymmetries might play an even larger role for the developments of FHAs in this group. Another interesting question related to pathology is whether analyzing the interactions between gray matter asymmetries, structural properties of callosal subsegments and intrahemispheric white matter asymmetries yields a greater insight into atypical lateralization in pathologies (e.g. schizophrenia) than looking at those structural properties in isolation. Last but not least, the theory also makes interesting implications regarding the evolution of FHAs. Given that the corpus callosum is a novel constituent of the mammalian brain, FHAs that exist in many vertebrates without a

corpus callosum (e.g. marsupialia, birds, reptiles, amphibians, fishes) intrahemispheric pathway asymmetries are likely to play an even bigger role for the emergence of FHAs in these animals than in humans. While data in birds support such an idea (Ocklenburg and Güntürkün, 2012), in many other organisms, the relation of intrahemispheric white matter asymmetries and FHAs has not been investigated, yet.

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