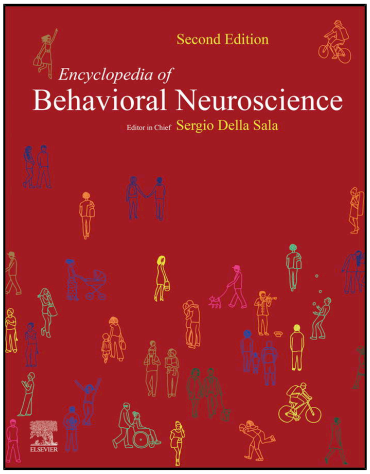

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White Matter Variability, Cognition, and Disorders

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Glossary

Inter-individual differences Variations in the structure and/or function of the brain

Tract bias Tract bias here means that the pathways that yield the greatest numbers of correlations with behavior are not necessarily those with the highest sensitivity for specific cognitive functions and pathologies

Tract-function correlation Correlation between functional measures and white matter pathways.

White matter phenotypes Inter-individual differences manifest as phenotypic appearances (e.g., eye color) driven by genetic phenotypes. White matter phenotypes describe the differences in the anatomy of brain connections.

Variability and Phenotypes

If one stopped in a busy street and observed the passers-by, one would be hard-pressed not to observe that people are different. These differences in appearance, opinions, creativity and morals have created the richness of society. Individuals of different races, ethnicities, religious beliefs, socioeconomic status, language and geographical origins have formed an inclusive and diverse community. In the medical world, inter-individual differences have long been a topic of study, and manifest as phenotypic appearances (e.g., eye color) driven by genetic phenotypes. For example, depending on our phenotype encoded by certain genes, we have different blood types or metabolic rates for drug absorption (e.g., McDonnell and Dang, 2013). Interindividual differences help to inform treatment procedures and accounting for them has already greatly improved patient outcomes and saved lives. Within any given population, there are potentially multiple sources of phenotypic variation. However, when turning to differences in brain anatomy, these inter-individual variations are relatively understudied (Glasser et al., 2016). Although it is well known that there are inter-individual differences in brain anatomy (e.g., Hirsch, 1963; Ono et al., 1990), the possibility of studying such variability across large populations and associating it with functional correlates has only become possible relatively recently, with the advent of non-invasive neuroimaging methods (Kanai and Rees, 2011). The current neuroimaging literature is primarily based on the assumption that all brains are the same. Most results are depicted as group averages on template brains where inter-individual variability is merely seen as a deviation from the mean or considered to be a pathological change. Certainly, employing an atlas-based approach is a valid method from a neuroimaging perspective, yet it has limitations in taking into account potentially relevant anatomical variability.

Studying Variability With Tractography

Studying inter-individual differences in the living human brain on a large scale has produced intriguing results so far. Neuroimaging sequences are highly sensitive for measuring the structure and function of the brain, both of which vary between individuals (Grasby et al., 2020; Tavor et al., 2016). On a structural level, measures of cortical surface area and thickness vary considerably within the population (Kong et al., 2018). Brain morphology is also not consistent across individuals: for example, half of the population have

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an additional gyrus above the cingulate, the paracingulate gyrus, in at least one hemisphere (Fornito et al., 2008). Even regions with clearly defined functions such as primary motor, auditory and visual cortices, are subject to anatomical variations (Uylings et al., 2005; Caulo et al., 2007; Leonard et al., 1998; Eichert et al., under review). Likewise, the most prominent language-relevant area in the inferior frontal gyrus is an area of high inter-individual variability in terms of its cytoarchitectonic boundaries (Amunts et al., 1999). This body of literature indicates a large amount of structural variability exists in primary cortical areas and associative cortices, but it is as yet unclear how these structural alterations relate to observable behavior and cognitive measures.

A better understanding of variability is crucial to better recognize the underlying neuronal scaffold. While the cerebral white matter may not be a functional agent *per se* (see Innocenti, 2017; Rockland, 2020 for discussion), it constrains the brain's functional organization (Bouhali et al., 2014; Thiebaut de Schotten and Shallice, 2017) and leads to functional impairment or complete loss of function when severed (Geschwind et al., 1965a, b). Hence the study of the cerebral white matter, or connectional anatomy, may be an ideal surrogate measure to capture inter-individual variability in structure and function. In the last 15 years, diffusion tractography has become an established non-invasive quantitative method to study connectional anatomy in the living human brain (for reviews see Assaf et al., 2017; Jbabdi and Johansen-Berg, 2011). Tractography has widely been employed as a neuroimaging biomarker to link white matter phenotypes to cognition and clinical presentations and these inter-individual differences are beginning to explain the observed variance in cognitive and behavioral measures. Phenotypes in this instance are considered to be interindividual variability in the appearance and structure of white matter networks. Phenotypes are defined as the product of an environment-genotype interaction. White matter tracts, and in particular language and limbic networks, have been shown to be sensitive to such interactions (Su et al., 2020; Budisaljevic et al., 2015, 2016). Consequently, white matter is subject to natural variations over the lifespan and changes as a result of training (Scholz et al., 2009; Lebel et al., 2019; Thiebaut de Schotten et al., 2012; Vanderauwera et al., 2018). Tractography has been shown to be highly sensitive for capturing these variations, which can be associated with interindividual differences in neuropsychological measures in the healthy population (e.g., Catani et al., 2007; Thiebaut de Schotten et al., 2011a,b; Howells et al., 2018) and clinical cohorts (e.g., Forkel et al., 2014a; Forkel et al., 2020; Thompson et al., 2017; Pacella et al., 2019). Tractography can, therefore, be employed as a method to study variability in the human brain and map the functional white matter correlates.

Finding consistent trends in the knowledge acquired from tractography studies is crucial to map white matter phenotypes and their impact on cognition, hence a systematic review is timely. We particularly focused on studies that describe significant correlations between structural and continuous cognitive measures in adults. For structure, we focused on volumetric or microstructural (e.g., fractional anisotropy, mean diffusivity etc.) measures of white matter pathways extracted from diffusion tractography. For behavioral measures, we focused on scores on neuropsychological tests or clinical scales in both healthy and clinical populations. We summarize dimensional differences in structural connectivity in relation to cognition as a step toward the systematic inclusion of inter-individual variability in neuroscience studies. The methodological details of this review can be found in Forkel et al. (2020).

The Number of Correlations and Studies Per Tract

In the current literature, a total of 25 individual tracts were reported to correlate with performance on neuropsychological tests or clinical symptoms (Fig. 1). Among these, certain pathways were more commonly correlated with cognitive-behavioral measures than others (Fig. 1A). We report here the number of studies that report a given correlation (Fig. 1A), but also the number of correlations per tract, which show a different pattern (Fig. 1B). This is important as in certain studies, more than one tract correlation was

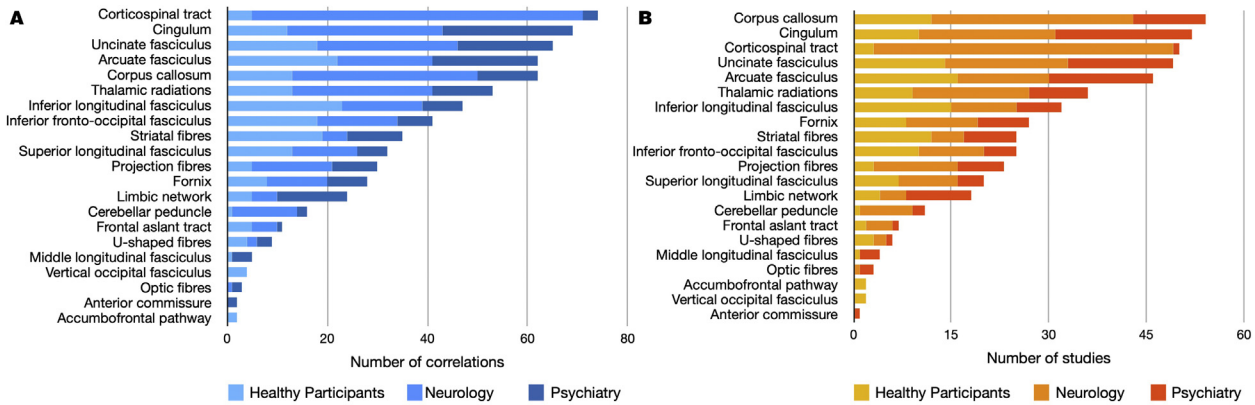

Fig. 1 Frequencies of reported correlations (A) and the number of studies (B) per tract in each field of study (i.e., healthy participants, neurology, psychiatry). A high number of correlations indicates a high tract sensitivity and a high number of studies represents high tract popularity. Note: Where tracts have multiple branches, they are only shown under the umbrella name (e.g., three segments of the arcuate fasciculus are shown as arcuate).

reported. Importantly, the most reported tracts (i.e., sensitivity) were not always those that were most systematically studied (i.e., popularity) indicated by the different number of studies per tract reported (Fig. 1B).

Our review shows that the majority of correlations and studies have been conducted in patients with neurological or psychiatric pathologies rather than controls (Fig. 1). Additionally, different tracts have been reported to correlate with measures classically obtained within each of these groups. For example, most correlations reported in healthy participants were with the inferior longitudinal fasciculus, arcuate fasciculus, and striatal fibers (Fig. 2A). In the neurological groups, most results were described for the corticospinal tract, the corpus callosum, and the cingulum (Fig. 2B). The cingulum, arcuate fasciculus, and uncinate fasciculus were the most commonly reported tracts to correlate with psychiatric symptoms (Fig. 2C). The most correlated (i.e., sensitivity), however, does not mean the most commonly studied pathways (i.e., popularity). In healthy participants, the most popular tracts were the arcuate fasciculus, inferior longitudinal fasciculus, and uncinate fasciculus (Fig. 2D). For the neurological group, the most studied tracts were the same as the most correlated tracts (Fig. 2E). In the psychiatric group, the order of the most studied tracts differed from the most correlated tracts and showed the highest load for the cingulum, arcuate fasciculus and uncinate (Fig. 2F).

The number of correlations per domains of interest. The analysis of the studied domains and the correlated pathways identified there was no one-to-one correspondence between white matter tracts and their domains (Fig. 3). The pathways with the clearest selectivity

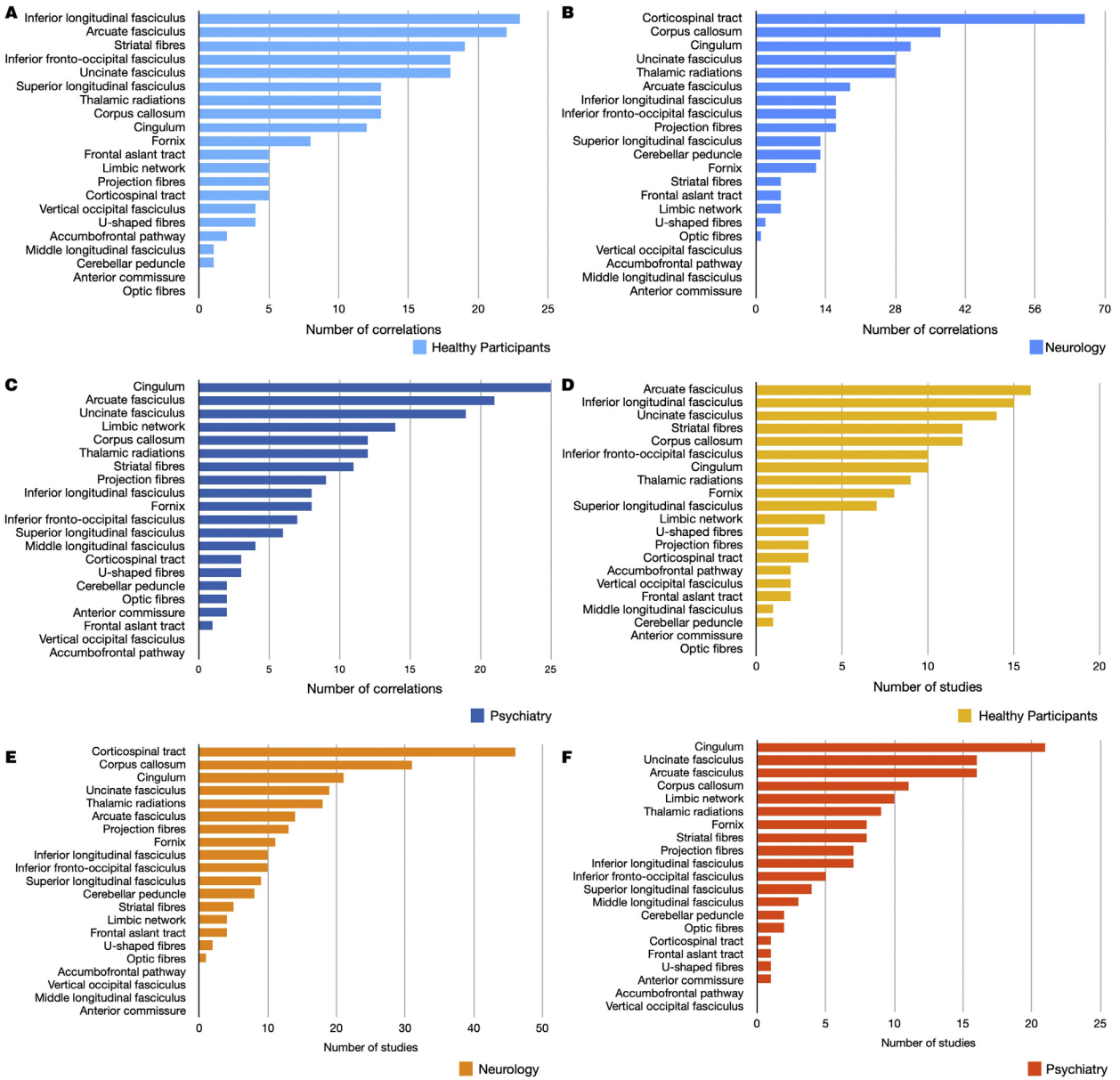

Fig. 2 "Tract bias" in the literature. Frequencies of tract sensitivity (A–C) and tract popularity (D–F) in healthy participants, neurology and psychiatry.

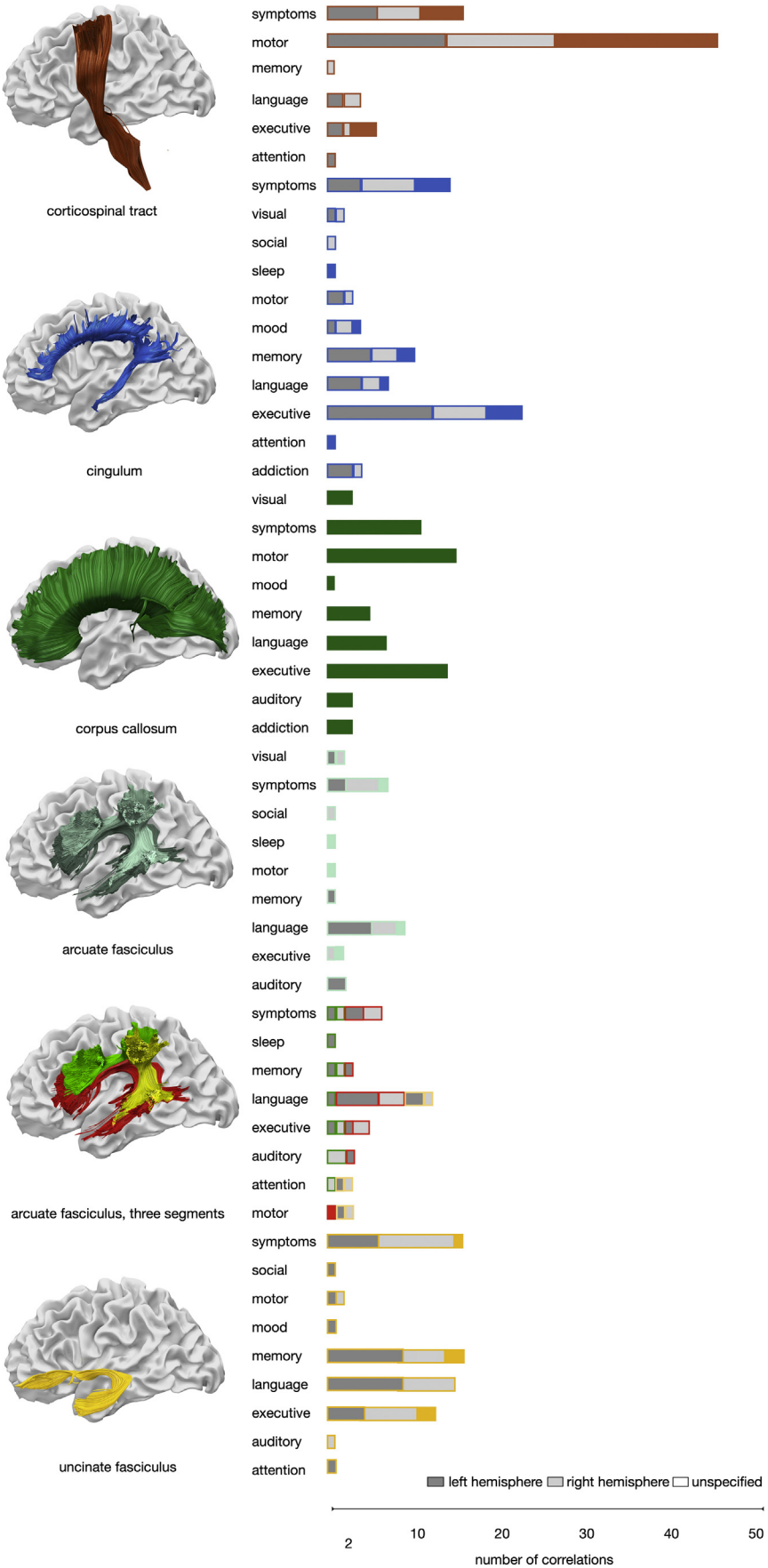

Fig. 3 Tract domain specificity. The number of correlations between cognitive, behavioral or clinical assessments and white matter tracts reveals that the concept of 'one tract-one function' does not hold true. The figure shows the most studied tracts.

to one domain were the corticospinal tract for the motor domain and the cingulum for measures of executive functions (Fig. 3). The level of selectivity to one domain is also often related to the diversity of projection of the tract. For instance, the corpus callosum, which projects on most of the surface of the brain (Karolis et al., 2019) was reported to be associated with all domains. Smaller tracts such as the entire arcuate fasciculus were also reported to be involved in all domains but with a stronger load on language measures and aphasic symptoms. To test the hypothesis that specificity of the domains of correlation might be driven by the level of precision of the dissection of the tracts, we further analyzed correlation results reported for the three individual segments of the arcuate fasciculus. This analysis revealed that the higher domain specificity of the overall arcuate with language was mainly driven by the long segment, while the other segments had a stronger load on memory and attention (Fig. 3).

Hemispheric specialization. The analysis highlighted that the current body of literature is inconsistently specifying the studied hemisphere explicitly. Among the 326 resources, a total of 674 significant tract-function correlations were reported. Within this data pool, an equal amount of studies specified if their correlations referred to the left hemisphere (37.38%) or the right hemisphere (35.01%), while the remaining results 27.60% (n = 186) were unspecified. Within the latter group, 64 results were reporting correlation with commissural tracts where the hemisphere may not be as relevant. The remaining results, however, which represent 122 of 674 correlations (18.10%) were describing association tracts (n = 45; 6.68%) or projection fibers (n = 77; 11.42%) where it would indeed make a difference if the correlations are reported within one or the other hemisphere.

Our analysis on the remaining results identified that some functions might be dominant in one hemisphere typically concerning the language domain for the left hemisphere and the arcuate fasciculus but also executive functions and the right cingulum and the right uncinate fasciculus (Fig. 3).

The last 15 years of investigation on correlations between white matter tracts and functions have yielded 326 studies in human adults. These correlations indicate the existence of inter-individual differences in healthy participants and across brain pathologies. Our systematic review of these findings highlights three main observations. Tractography has been used to study inter-individual variability in many populations and has proven to be a sensitive method in neurology, psychiatry and healthy populations to identify variability and its functional correlates. Secondly, we observed that there is a "tract bias" in the literature, meaning that the pathways that yield the greatest numbers of correlations with behavior are not necessarily those with the highest sensitivity for specific cognitive functions and pathologies. Finally, our review demonstrates that tracts, as we define them, are not usually correlated with only one, but rather multiple cognitive domains or pathologies.

Tractography as a Tool to Measure Variability

Our investigation objectively collated tract-function correlations across neurological, psychiatric and healthy populations. However, more results were reported in pathological cohorts than in healthy participants (Fig. 1). The dominance of pathological cohorts in the field of correlational tractography may originate from the broader dispersity of the data points associated with pathology. Indeed, the presence of pathology causes higher variability in both structure and function, which is more likely to be detected with a linear correlation and could have produced a publication bias. Another consideration may be that differences between healthy participants are considered to be noise by most research teams. While noise may contribute to the difference observed in controls it is now clearly established that diffusion-weighted imaging tractography can capture inter-individual differences that reflect some of the variations in the functioning of the brain (e.g., Powell et al., 2006; Vernooij et al., 2007 for language lateralization). An alternative hypothesis could be that current neuroimaging methods or cognitive and behavioral tests are not sensitive enough to systematically disentangle noise from true variability in healthy participants. The latter may be improved by using finer-grained cognitive measures, higher resolution data, and better anatomical tract definitions.

Tract Domain Specificity

Some pathways were clearly more sensitive than others. Our review identified a total of 25 tracts that were significantly correlated with cognitive measures or symptom severity in clinical cohorts and healthy participants. While the precise number of white matter tracts in the human brain remains unknown and changes depending on the methods used, current atlases indicate a total of around 26 tracts that can be reliably identified with most tractography methods (Mori et al., 2005; Lawes et al., 2008; Catani and Thiebaut de Schotten, 2008; Mori et al., 2009; Thiebaut de Schotten et al., 2011a,b; Rojkova et al., 2016) with some recent atlases further identifying additional intralobar connections (Catani et al., 2012, 2017; Guevara et al., 2012, 2020). Some pathways identified by our systematic review have not even been incorporated into atlases, which includes the accumbofrontal tract and the vertical occipital fasciculus (Martínez-Molina et al., 2019; Rigoard et al., 2011; Vergani et al., 2014, 2016; Yeatman et al., 2013). This discrepancy between our findings and current atlases highlights a potential tract bias in the literature toward studying specific pathways that either have very well-established functions (e.g., corticospinal tract, arcuate fasciculus) or easy to dissect in clinical cohorts (e.g., cingulum). This, however, does not necessitate that the other tracts are not functionally relevant or might show correlations with other non-routinely tested cognitive and behavioral measures. Some of these understudied pathways may be more challenging to reconstruct due to limited anatomical guidelines or available algorithms (e.g., U-shaped fibers, Attar et al., 2020) or they may be harder to reconstruct (Mandelstam, 2012; Maffei et al., 2019a, 2019b).

'One-Tract One-Function' Myth

For the most sensitive tracts, several functions were reported. Even the corticospinal tract, which was primarily studied within the motor domain (62.21% of correlations, Fig. 3), presented with a non-uniform functional profile. For instance, some studies reported associations of the corticospinal tract with executive functions (8.11%) and language/speech processes (5.4%). For other tracts, the correlations were even more diverse. For example, the cingulum correlated with psychiatric symptom severity (20.29%), memory (14.49%) and language measures (10.14%). Such results could support the idea of a hierarchical brain organization with some tracts involved in mediating many functions, whereas others are more specific, although this requires dedicated study (Pandya and Yeterian, 1990). While the number of associations is likely to be biased by a number of factors including prior hypotheses that a given tract is involved in a specific function, a complementary study has recently mapped 590 cognitive functions, as defined by a meta-analysis of BOLD activation derived from fMRI paradigms, onto an extensive white matter atlas (Thiebaut de Schotten et al., 2020). This functional white matter atlas reveals similar findings as observed in our data and highlights that one pathway can be relevant for multiple functions. Another possible interpretation of this finding would be that the definition of white matter tracts as we know it is too coarse to be specific to only one given function. As shown in our result, the three segments of the arcuate fasciculus (Catani et al., 2005) were more domain-specific than the entire arcuate fasciculus. This calls for a finer-grained white matter division or more data-driven approaches to identify the portion of white matter related to specific functions (see for example Foulon et al., 2018).

In addition, there is a differential pattern emerging between healthy participants and pathological groups. One such example is the uncinate fasciculus that has been primarily associated with memory in healthy aging (Sasson et al., 2013), with psychopathy in psychiatric studies (e.g., Craig et al., 2009), and language in neurological studies (e.g., D'Anna et al., 2016). Similarly, the arcuate fasciculus has been implicated in learning new words in healthy participants (López-Barroso et al., 2013), auditory hallucinations in schizophrenia (Catani et al., 2011), and aphasia severity after stroke (Forkel et al., 2014a). The functions associated with a pathway might therefore not purely be a product of the cortical regions the white matter connects to but rather rely on the interplay of one region with another. When pathology is introduced into this delicate network, for example by a lesion, the differential symptom pattern may reflect effects on different brain regions that are weighted differently. Furthermore, the pathophysiological mechanisms are different across pathologies and have different long-range effects on connected regions (for a review see Catani and Ffytche, 2005).

Limitations

There are tractography limitations that may have influenced the studies. First, it is important to remember what tractography can and cannot do when interpreting results. While tractography has proven useful for research and clinical applications, the interpretation of voxel-based indices presents challenges (Dell'Acqua and Tournier, 2019). For example, diffusion indices are averaged across and within voxels, which may mask meaningful changes. For research acquisitions, the voxel size is typically 2*2*2 mm, while the voxel sizes are often larger for clinical data leading to even lower spatial resolution. An 8 mm^3 voxel is likely to contain an inhomogeneous sample of tissue classes, intra- and extracellular space, and axons of different density and diameter, which poses particular challenges for the study of projection and commissural fibers. The diffusion signal is also inhomogeneous across the brain, and areas such as the orbitofrontal cortex and anterior temporal cortex are often distorted. Methodological advances, however, partially correct for these distortions and disentangle some of these components and crossing fibers to extract tract-specific measurements (see Dell'Acqua and Tournier, 2019). While recent research studies have methodological means to mitigate such distortions (e.g., TOPUP, Andersson et al., 2003), most current clinical studies still suffer from these limitations thus potentially explaining the lack of tract-domain specificity.

Another source of inconsistencies originates from incoherent reporting of the anatomy. For example, 18% of records did not specify which hemisphere was studied or collapsed their white matter measures across both hemispheres and correlated this average with behavior. Collapsing measurements from anatomical feature across both hemispheres might prove problematic for white matter pathways that are subject to larger inter-individual variability and might get over- and underrepresented in each hemisphere (e.g., Catani et al., 2007; Thiebaut de Schotten et al., 2011a,b; Rojkova et al., 2016, Croxson et al., 2018; Howells et al., 2020). Further, while the concept of a strict hemispheric dichotomy might be seen as overly simplistic (e.g., Vingerhoets, 2019), splitting the measurements by hemisphere may reveal useful insights and higher specificity into the contribution of either side to a measured cognitive behavior. Another limitation comes from the inconsistencies in the classification of white matter pathways. For instance, the superior longitudinal fasciculus (SLF) was often considered without specifying which branch was studied. When the branches were specified, there was a variety of terminologies, including the three branches SLFI-III (Thiebaut de Schotten et al., 2011a,b), or a lobar separation of an SLFtp (temporal projections) and SLFpt (parietal projections) (e.g., Nakajima et al., 2019). Similarly, the arcuate was either considered in its entirety or was split into several branches, classified as the long, anterior, and posterior segments or the horizontal and vertical branches (e.g., Catani et al., 2005; Kaplan et al., 2010). Originating from early anatomical papers, we are still faced with a body of literature that uses the terms SLF and arcuate interchangeably. While there is some overlap between both networks, for example between the SLF-III and the anterior segment of the arcuate fasciculus, other branches and segments are distinct. From an anatomical and etymological perspective, the superior longitudinal fasciculus should be considered to be solely those fibers connecting frontal and parietal regions (i.e., "superior and longitudinal"; Thiebaut de Schotten et al., 2011a,b)

whereas the arcuate fasciculus should be considered to be the fronto-temporal connection (i.e., 'arcuatus' translates to 'arching' around the Sylvian fissure; Catani et al., 2005). Another example is the differential and synonymous use of the terminologies external capsule (Rilling et al., 2012), external/extreme fiber complex (Mars et al., 2016), inferior fronto-occipital fasciculus (Forkel et al., 2014b), and inferior occipitofrontal fasciculus (Kier et al., 2004). The difference in terminology is largely owed to the description of these pathways using different methods (Forkel et al., 2014b) and a consensus is needed (Maier-Hein et al., 2017; Mandonnet et al., 2018).

Additionally, to harvest these interindividual variability results, this review focused on continuous measures to associate white matter phenotypes with cognition and clinical symptoms. As such, we did not separate biological subtypes (e.g., Ferreira et al., 2020; Forkel et al., 2020) and did not take different diffusion matrices (e.g., fractional anisotropy and mean diffusivity) or tractography algorithms (e.g., deterministic and probabilistic) into account. Some of these parameters might be more sensitive and specific than others but some were underrepresented in our systematic review preventing any valid comparison. Finally, while correlational research indicates that there may be a relationship between two variables (e.g., structure and function), it cannot prove that one variable causes a change in another variable. This means that it is impossible to determine from this type of data whether anatomical variability is driving behavior or if the anatomy is a result of an expressed behavior (i.e., the directionality problem). It is also not possible to know whether a third factor is mediating the changes in both variables and that in fact the two variables are not related (i.e., the 'third variable problem'). While this question is beyond the scope of the current study, ideally, future research could explore another statistical framework to assess causal relationships between the variables (Pacella et al., 2019).

All in all, acknowledging and objectively quantifying the degree of variability between each of us, particularly when it comes to brain anatomy, will potentially have a far-reaching impact on clinical practice. While some methodological refinement is needed in the field of white matter tractography (Wasserthal et al., 2018; Maier-Hein et al., 2017), preliminary evidence indicates that variations in white matter anatomy can show disease progression or explain differential patterns of symptoms (Forkel et al., 2020). Differences in brain connections can also shed light on why current invasive and non-invasive treatments and therapies are helping some but not all patients (Lunven et al., 2019; Parlatini et al., under review; Sanefuji et al., 2017). These findings are encouraging, as we move toward personalized medicine. Tract-function correlations, with the improvements suggested in this systematic review, could be the right candidate to predict resilience and recovery in patients.

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References

Amunts, K., Schleicher, A., Bürgel, U., Mohlberg, H., Uylings, H., Zilles, K., 1999. Broca's region revisited: cytoarchitecture and intersubject variability. J. Comp. Neurol. 412, 319–341.

Andersson, J.L.R., Skare, S., Ashburner, J., 2003. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. Neuroimage 20 (2), 870–888.

Assaf, Y., Johansen-Berg, H., Thiebaut de Schotten, M., 2017. The role of diffusion MRI in neuroscience. NMR Biomed. https://doi.org/10.1002/nbm.3762.

Attar, F.M., Kirilina, E., Haenelt, D., Pine, K.J., Trampel, R., Edwards, L., et al., 2020. Mapping short association fibers in the early cortical visual processing stream using in vivo diffusion tractography. Cerebr. Cortex. https://doi.org/10.1093/cercor/bhaa049.

Bouhali, F., Thiebaut de Schotten, M., Pinel, P., Poupon, C., Mangin, J.F., Dehaene, S., Cohen, L., 2014. Anatomical connections of the visual word form area. J. Neurosci. 34 (46), 15402–15414.

Budisavljevic, S., Dell'Acqua, F., Rijsdijk, F.V., Kane, F., Picchioni, M., McGuire, P., et al., 2015. Age-related differences and heritability of the Perisylvian language networks. J. Neurosci. 35 (37), 12625–12634.

Budisavljevic, S., Kawadler, J.M., Dell'Acqua, F., Rijsdijk, F.V., Kane, F., Picchioni, M., et al., 2016. Heritability of the limbic networks. Soc. Cognit. Affect Neurosci. 5, 746–757.

Catani, M., Allin, M.P.G., Husain, M., Pugliese, L., Mesulam, M.-M., Murray, R.M., et al., 2007. Symmetries in human brain language pathways correlate with verbal recall. Proc. Natl. Acad. Sci. U.S.A. 104 (43), 17163–17168.

Catani, M., Craig, M.C., Forkel, S.J., Kanaan, R., Picchioni, M., Toulopoulou, T., Shergill, S., Williams, S., Murphy, D.G., McGuire, P., 2011. Altered integrity of Perisylvian language pathways in schizophrenia: relationship to auditory hallucinations. Biol. Psychiatry 70 (12), 1143–1150.

Catani, M., Dell'Acqua, F., Vergani, F., Malik, F., Hodge, H., Roy, P., et al., 2012. Short frontal lobe connections of the human brain. Cortex 48 (2), 273–291.

Catani, M., Ffytche, D., 2005. The rises and falls of disconnection syndromes. Brain 128 (10), 2224–2239.

Catani, M., Jones, D., Ffytche, D., 2005. Perisylvian language network of the human brain. Ann. Neurol. 57 (1), 8–16.

Catani, M., Robertsson, N., Beyh, A., Huynh, V., de Santiago Requejo, F., Howells, H., et al., 2017. Short parietal lobe connections of the human and monkey brain. Cortex 97, 339–357.

Catani, M., Thiebaut de Schotten, M., 2008. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. Cortex 44 (8), 1105–1132.

Caulo, M., Briganti, C., Mattei, P.A., Perfetti, B., Ferretti, A., Romani, G.L., et al., 2007. New morphologic variants of the hand motor cortex as seen with MR imaging in a large study population. Am. J. Neuroradiol. 28 (8), 1480–1485.

Craig, M., Catani, M., Deeley, Q., Latham, R., Daly, E., Kanaan, R., et al., 2009. Altered connections on the road to psychopathy. Mol. Psychiatry 14 (10), 946–953, 907.

Croxson, P.L., Forkel, S.J., Cerliani, L., Thiebaut de Schotten, M., 2018. Structural variability across the primate brain: a cross-species comparison. Cerebr. Cortex 28 (11), 3829–3841.

D'Anna, L., Mesulam, M.M., Thiebaut de Schotten, M., Dell'Acqua, F., Murphy, D., Wieneke, C., et al., 2016. Frontotemporal networks and behavioral symptoms in primary progressive aphasia. Neurology 86 (15), 1393–1399.

Dell'Acqua, F., Tournier, J.D., 2019. Modelling white matter with spherical deconvolution: how and why? NMR Biomed. 32 (4), e3945.

Eichert, N., Watkins, K.E., Mars, R.B., Petrides, M. Morphological and functional variability in central and subcentral motor cortex of the human brain. BioRxiv. https://doi.org/10.1101/2020.03.17.995035.
Ferreira, D., Nordberg, A., Westman, E., 2020. Biological subtypes of Alzheimer disease: a systematic review and meta-analysis. Neurology 94 (10), 436–448.
Forkel, S.J., Rogalski, E., Drossinos Sancho, N., D'Anna, L., Luque Laguna, P., Sridhar, J., Dell'Acqua, F., et al., 2020. Anatomical evidence of an indirect pathway for word repetition. Neurology 94 (6), e594–e606.
Forkel, S.J., Thiebaut de Schotten, M., Dell'Acqua, F., Kalra, L., Murphy, D.G., Williams, S.C., et al., 2014a. Anatomical predictors of aphasia recovery: a tractography study of bilateral Perisylvian language networks. Brain 137 (Pt 7), 2027–2039.
Forkel, S.J., Thiebaut de Schotten, M., Kawadler, J.M., Dell'Acqua, F., Danek, A., Catani, M., 2014b. The anatomy of fronto-occipital connections from early blunt dissections to contemporary tractography. Cortex 56, 73–84.
Fornito, A., Wood, S.J., Whittle, S., Fuller, J., Adamson, C., Saling, M.M., et al., 2008. Variability of the paracingulate sulcus and morphometry of the medial frontal cortex: associations with cortical thickness, surface area, volume, and sulcal depth. Hum. Brain Mapp. 29 (2), 222–236.
Foulon, C., Cerliani, L., Kinkingnéhun, S., Levy, R., Rosso, C., Urbanski, M., et al., 2018. Advanced lesion symptom mapping analyses and implementation as BCBtoolkit. GigaScience 7 (3), giy004.
Geschwind, N., 1965a. Disconnexion syndromes in animals and man. I. Brain 88 (2), 237–294. https://doi.org/10.1093/brain/88.2.237. PMID: 5318481.
Geschwind, N., 1965b. Disconnexion syndromes in animals and man. II. Brain 88 (3), 585–644. https://doi.org/10.1093/brain/88.3.585. PMID: 5318824.
Glasser, M.F., Coalson, T.S., Robinson, E.R., Hacker, C.D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C.F., Jenkinson, M., Smith, S.M., Van Essen, D.C., 2016. A multi-modal parcellation of the human cerebral cortex. Nature 536, 171–178.
Grasby, K., Jahanshad, N., Painter, J.N., Colodro-Conde, L., Bralten, J., Hibar, D.P., et al., 2020. The genetic architecture of the human cerebral cortex. Science 367 (6484), eaay6690.
Guevara, M., Guevara, P., Román, C., Mangin, J.F., 2020. Superficial white matter: a review on the dMRI analysis methods and applications. Neuroimage 212. https://doi.org/10.1016/j.neuroimage.2020.116673.
Guevara, P., Duclap, D., Poupon, C., Marrakchi-Kacem, L., Fillard, P., Le Bihan, D., et al., 2012. Automatic fiber bundle segmentation in massive tractography datasets using a multi-subject bundle atlas. Neuroimage 61 (4), 1983-1099.
Hirsch, J., 1963. Behavior genetics and individuality understood. Science 142 (3598), 1436–1442.
Howells, H., Thiebaut de Schotten, M., Dell'Acqua, F., Beyh, A., Zappalà, G., Leslie, A., Simmons, A., et al., 2018. Frontoparietal tracts linked to lateralized hand preference and manual specialization. Cerebr. Cortex 28 (7), 2482–2494.
Howells, H., Puglisi, G., Leonetti, A., Vigano, L., Fornia, L., Simone, L., et al., 2020. The role of left fronto-parietal tracts in hand selection: evidence from neurosurgery. Cortex. https://doi.org/10.1016/j.cortex.2020.03.018.
Innocenti, G.M., 2017. Network causality, axonal computations, and Poffenberger. Exp. Brain Res. 235, 2349–2357.
Jbabdi, S., Johansen-Berg, H., 2011. Tractography: where do we go from here? Brain Connect. 1 (3), 169–183.
Kanai, R., Rees, G., 2011. The structural basis of inter-individual differences in human behaviour and cognition. Nat. Rev. Neurosci. 12 (4), 231–242.
Kaplan, E., Naeser, M.A., Martin, P.I., Ho, M., Wang, Y., Baker, E., Pascual-Leone, A., 2010. Horizontal portion of arcuate fasciculus fibers track to pars opercularis, not pars triangularis, in right and left hemispheres: a DTI study. Neuroimage 52 (2), 436–444.
Karolis, V., Corbetta, M., Thiebaut de Schotten, M., 2019. The architecture of functional lateralisation and its relationship to callosal connectivity in the human brain. Nat. Comm. 10, 1417.
Kier, E.L., Staib, L.H., Davis, L.M., Bronen, R.A., 2004. MR imaging of the temporal stem: anatomic dissection tractography of the uncinate fasciculus, inferior occipitofrontal fasciculus, and Meyer's loop of the optic radiation. AJNR Am. J. Neuroradiol. 25 (5), 677–691. PMID: 15140705, PMCID: PMC7974480.
Kong, X.Z., Mathias, S.R., Guadalupe, T., ENIGMA Laterality Working Group, Glahn, D.C., Franke, B., et al., 2018. Mapping cortical brain asymmetry in 17,141 healthy individuals worldwide via the ENIGMA Consortium. Proc. Natl. Acad. Sci. U.S.A. 115 (22), E5154–E5163.
Lawes, I.N., Barrick, T.R., Murugam, V., Spierings, N., Evans, D.R., Song, M., et al., 2008. Atlas-based segmentation of white matter tracts of the human brain using diffusion tensor tractography and comparison with classical dissection. Neuroimage 39 (1), 62–79.
Lebel, C., Treit, S., Beaulieu, C., 2019. A review of diffusion MRI of typical white matter development from early childhood to young adulthood. NMR Biomed. 32 (4), e3778.
Leonard, C.M., Puranik, C., Kuldau, J.M., Lombardino, L.J., 1998. Normal variation in the frequency and location of human auditory cortex landmarks. Heschl's gyrus: where is it? Cerebr. Cortex 8 (5), 397–406.
López-Barroso, D., Catani, M., Ripollés, P., Dell'Acqua, F., Rodríguez-Fornells, A., de Diego-Balaguer, R., 2013. Word learning is mediated by the left arcuate fasciculus. Proc. Natl. Acad. Sci. U.S.A. 110 (32), 13168–13173.
Lunven, M., Rode, G., Bourlon, C., Duret, C., Migliaccio, R., Chevrillon, E., et al., 2019. Anatomical predictors of successful prism adaptation in chronic visual neglect. Cortex 120, 629–641.
Maffei, C., Sarubbo, S., Jovicich, J., 2019a. A missing connection: a review of the macrostructural anatomy and tractography of the acoustic radiation. Front. Neuroanat. 13, 27.
Maffei, C., Sarubbo, S., Jovicich, J., 2019b. Diffusion-based tractography atlas of the human acoustic radiation. Sci. Rep. 9, 4046.
Maier-Hein, K., Neher, P.F., Houde, J.C., Côte, M.A., Garyfallidis, E., Zhong, J., 2017. The challenge of mapping the human connectome based on diffusion tractography. Nat. Commun. 8, 1349.
Mandelstam, S.A., 2012. Challenges of the anatomy and diffusion tensor tractography of the meyer loop. Am. J. Neuroradiol. 33, 1204–1210.
Mandonnet, E., Sarubbo, S., Petit, L., 2018. The nomenclature of human white matter association pathways: proposal for a systematic taxonomic anatomical classification. Front. Neuroanat. 12, 94.
Mars, R.B., Foxley, S., Verhagen, L., Jbabdi, S., Sallet, J., Noonan, M.P., et al., 2016. The extreme capsule fiber complex in humans and macaque monkeys: a comparative diffusion MRI tractography study. Brain Struct. Funct. 221 (8), 4059–4071.
Martínez-Molina, N., Mas-Herrero, E., Rodríguez-Fornells, A., Zatorre, R.J., Marco-Pallarés, J., 2019. White matter microstructure reflects individual differences in music reward sensitivity. J. Neurosci. 39 (25), 5018–5027.
McDonnell, A.M., Dang, C.H., 2013. Basic review of the cytochrome P450 system. J. Adv. Pract. Oncol. 4 (4), 263–268.
Mori, S., Wakana, S., van Zijl, P.C.M., Nagae-Poetscher, L.M., 2005. MRI Atlas of Human White Matter. Elsevier, Amsterdam.
Mori, S., Oishi, K., Faria, A.V., 2009. White matter atlases based on diffusion tensor imaging. Curr. Opin. Neurol. 22 (4), 362–369.
Nakajima, R., Kinoshita, M., Shinohara, H., Nakada, M., 2019. The superior longitudinal fascicle: reconsidering the fronto-parietal neural network based on anatomy and function. Brain Imaging Behav. https://doi.org/10.1007/s11682-019-00187-4.
Ono, M., Kubik, S., Abernathey, C.D., 1990. Atlas of the Cerebral Sulci. Thieme, Stuttgart.
Pacella, V., Foulon, C., Jenkinson, P.M., Scandola, M., Bertagnoli, S., Avesani, R., et al., 2019. Anosognosia for hemiplegia as a tripartite disconnection syndrome. Elife 8, e46075. https://doi.org/10.7554/eLife.46075.
Pandya, D.N., Yeterian, E.H., 1990. Architecture and Connections of Cerebral Cortex: Implications for Brain Evolution and Function. The Guilford Press, New York.
Parlatini, V., Radua, J., Whickers, R., Maltezos, S., Sanefuji, M., Dell'Acqua, F., et al. The anatomy of attentive brain networks predicts response to stimulant treatment in adults with attention deficit hyperactivity disorder (ADHD). under review.
Powell, H.W.R., Parker, G.J.M., Alexander, D., Symms, M.R., Boulby, P.A., Wheeler-Kingshott, C.A.M., et al., 2006. Hemispheric asymmetries in language-related pathways: a combined functional MRI and tractography study. Neuroimage 32 (1), 388–399.

Rigoard, P., Buffenoir, K., Jaafari, N., Giot, J.P., Houeto, J.L., Mertens, P., et al., 2011. The accumbofrontal fasciculus in the human brain: a microsurgical anatomical study. Neurosurgery 68 (4), 1102–1111.
Rilling, J., Glasser, M., Jbabdi, S., Andersson, J., Preuss, T., 2012. Continuity, divergence, and the evolution of brain language pathways. Front. Evol. Neurosci. 3, 11.
Rockland, K.S., 2020. What we can learn from the complex architecture of single axons. Brain Struct. Funct. https://doi.org/10.1007/s00429-019-02023-3.
Rojkova, K., Volle, E., Urbanski, M., Humbert, F., Dell'Acqua, F., Thiebaut de Schotten, M., 2016. Atlasing the frontal lobe connections and their variability due to age and education: a spherical deconvolution tractography study. Brain Struct. Funct. 221 (3), 1751–1766.
Sanefuji, M., Craig, M., Parlatini, V., Mehta, M., Murphy, D.G., Catani, M., et al., 2017. Double-dissociation between the mechanism leading to impulsivity and inattention in attention deficit hyperactivity disorder: a resting-state functional connectivity study. Cortex 86, 290–302.
Sasson, E., Doniger, G.M., Pasternak, O., Tararasch, R., Assaf, Y., 2013. White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. Front. Neurosci. 7, 32.
Scholz, J., Klein, M.C., Behrens, T.E., Johansen-Berg, H., 2009. Training induces changes in white matter architecture. Nat. Neurosci. 12 (11), 1370–1371.
Su, M., Thiebaut de Schotten, M., Zhao, J., Song, S., Zhou, W., Gong, G., et al., 2020. Influences of the early family environment and long-term vocabulary development on the structure of white matter pathways: a longitudinal investigation. Dev. Cogn. Neurosci. 42, 100767.
Tavor, I., Parker Jones, O., Mars, R.B., Smith, S.M., Behrens, T.B., Jbabdi, S., 2016. Task-free MRI predicts individual differences in brain activity during task performance. Science 352 (6282), 216–220.
Thiebaut de Schotten, M., Shallice, T., 2017. Identical, similar or different? Is a single brain model sufficient? Cortex 86, 172–175.
Thiebaut de Schotten, M., Cohen, L., Amemiya, E., Braga, L.W., Dehaene, S., 2012. Learning to read improves the structure of the arcuate fasciculus. Cerebr. Cortex 24 (4), 989–995.
Thiebaut de Schotten, M., Dell'Acqua, F., Forkel, S.J., Simmons, A., Vergani, F., et al., 2011a. A lateralized brain network for visuospatial attention. Nat. Neurosci. 14 (10), 1245–1246.
Thiebaut de Schotten, M., ffytche, D.H., Bizzi, A., Dell'Acqua, F., Allin, M., Walshe, M., et al., 2011b. Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. Neuroimage 54 (1), 49–59.
Thiebaut de Schotten, M., Foulon, C., Nachev, P., 2020. Brain disconnections link structural connectivity with function and behaviour. Nat. Commun. 11 https://doi.org/10.1038/s41467-020-18920-9.
Thompson, A., Murphy, D., Dell'Acqua, F., Ecker, C., McAlonan, G., Howells, H., et al., 2017. Impaired communication between the motor and somatosensory homunculus is associated with poor manual dexterity in autism spectrum disorder. Biol. Psychiatry 81 (3), 211–219.
Uylings, H.B.M., Rajkowska, G., Sanz-Arigita, E., Amunts, K., Zilles, K., 2005. Consequences of large interindividual variability for human brain atlases: converging macroscopical imaging and microscopical neuroanatomy. Anat. Embryol. 210 (5–6), 423–431.
Vanderauwera, J., De Vos, A., Forkel, S.J., Catani, M., Wouters, J., Vandermosten, M., Ghesquière, P., 2018. Neural organization of ventral white matter tracts parallels the initial steps of reading development: a DTI tractography study. Brain Lang. 183, 32–40.
Vergani, F., Mahmood, S., Morris, C., Mitchell, P., Forkel, S.J., 2014. Intralobar fibres of the occipital lobe: a post mortem dissection study. Cortex 56, 145–156.
Vergani, F., Martino, J., Morris, C., Attems, J., Ashkan, K., Dell'Acqua, F., 2016. Anatomic connections of the subgenual cingulate region. Neurosurgery 79 (3), 465–472.
Vernooij, M.W., Smits, M., Wielopolski, P.A., Houston, G.C., Krestin, G.P., van der Lugt, A., 2007. Fiber density asymmetry of the arcuate fasciculus in relation to functional hemispheric language lateralization in both right- and left-handed healthy subjects: a combined fMRI and DTI study. Neuroimage 35 (3), 1064–1076.
Vingerhoets, G., 2019. Phenotypes in hemispheric functional segregation? Perspectives and challenges. Phys. Life Rev. 30, 1–18.
Wasserthal, J., Neher, P., Maier-Hein, K.H., 2018. TractSeg - fast and accurate white matter tract segmentation. Neuroimage 183, 239–253.
Yeatman, J.D., Rauschecker, A.M., Wandell, B.A., 2013. Anatomy of the visual word form area: adjacent cortical circuits and long-range white matter connections. Brain Lang. 125 (2), 146–155.