White matter variability, cognition, and disorders: a systematic review.

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Abstract

Inter-individual differences can inform treatment procedures and - if accounted for - have the potential to significantly improve patient outcomes. However, when studying brain anatomy, these inter-individual variations are commonly unaccounted for, despite reports of differences in gross anatomical features, cross-sectional and connectional anatomy. Brain connections are essential to facilitate functional organisation and, when severed, cause impairments or complete loss of function. Hence the study of cerebral white matter may be an ideal compromise to capture inter-individual variability in structure and function. We reviewed the wealth of studies that associate functions and clinical symptoms with individual tracts using diffusion tractography. Our systematic review indicates that tractography has proven to be a sensitive method in neurology, psychiatry and healthy populations to identify variability and its functional correlates. However, the literature may be biased, as we determined that the most commonly studied tracts are not necessarily those with the highest sensitivity to cognitive functions and pathologies. Additionally, the side of the studied tract is often unreported, thus neglecting functional laterality and hemispheric asymmetries. Finally, we demonstrate that tracts, as we define them, are not usually correlated with only one, but rather multiple cognitive domains or pathologies. While our systematic review identified some methodological caveats, it also suggests that tract-function correlations might be a promising biomarker for precision medicine. It characterises variations in brain anatomy, differences in functional organisation, and predicting resilience or recovery in patients.

Introduction

If one stopped in a busy street and observed passers-by, one cannot help but observe that people are physically different. This diversity in appearance but also opinions, creativity and morals has helped create a rich society. Individuals of different races, ethnicities, religious beliefs, socioeconomic status, language, and geographical origins make up our inclusive and diverse community. Ever-evolving changes in our genome and adaptation to environmental factors have contributed to a range of genotypes (variability in genetic code) and phenotypes (variability in observable traits, *e.g.* eye colour) and the interaction between them (White & Rabargo-Smith, 2011). In the medical world, studying these inter-individual differences has led to the new disciplines of personalised and precision medicine. Interindividual differences can help inform treatment procedures, and accounting for them has already improved patient outcomes and saved lives.

However, when turning to differences in brain anatomy, these inter-individual variations are relatively understudied (Glasser et al., 2016). Neuroscientists often assume that we share the same organisation of cognitive functions, and the same underlying brain anatomy (Caramazza, 1986; Goldin *et al.*, 2008; Greene *et al.*, 2004; Johnson-Frey, 2004; Treu *et al.*, 2020). 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. In contrast, neuroanatomical studies have reported variability in individual brain structures (*e.g.* Sachs, 1892; Ono *et al.*, 1990; Rademacher *et al.*, 1993; Amunts *et al.*, 1999, Caspers *et al.,* 2006; Fornito *et al.*, 2008), psychologists assume a Gaussian distribution of

cognition and behaviour (Seghier & Price, 2018), and clinicians report differences in susceptibility to disorders and recovery (Forkel *et al.,* 2014; Forkel *et al.,* 2020). Although these studies highlight the existence of structural and functional variability, the possibility of studying such variability across large populations and associating it with functional correlates has only emerged recently through the availability of unique datasets with critical sample sizes and advances in computing power (Kanai & Rees, 2011; Dubois & Adolphs, 2016). Neuroimaging sequences are highly sensitive for measuring the structure and function of the brain, both of which vary between individuals (Lerch et al., 2017; Gordon et al., 2017; Grasby et al., 2020; Tavor et al., 2016). On a structural level, measures of cortical surface area and thickness show hemispheric asymmetries that vary within the population (Kong et al. 2018). Brain morphology is also variable with half of the population having an additional gyrus, the paracingulate gyrus, in at least one hemisphere, for example (Fornito et al., 2008). Primary cortical regions such as the motor, auditory and visual cortices, are subject to anatomical variations (Uylings et al., 2005; Caulo et al., 2005; Leonard et al., 1998; Eichert et al., 2020) and associative cortical regions have variable cytoarchitectonic boundaries (Amunts et al., 1999). This body of literature indicates that a large amount of structural variability exists in primary cortical areas and associative cortices. Still, it is as yet unclear how these structural alterations relate to observable behaviour and cognitive measures.

There is a growing trend in the field to understand the structure-function relationship in the light of interindividual variability. Recent evidence has identified anatomical variations that are linked to differences in cognition and clinical outcomes (Forkel *et al.,* 2020; Harrisson *et al.*, 2020; Johnson *et al.*, 2020; Taebi *et al.*, 2020; Munsell *et al.*, 2020; Wang *et al.*, 2021). However, there has not yet been a systematic attempt to capture this variability across the entire brain and its connections and associate white matter variability phenotypes with cognitive profiles and clinical dimensions. It is, therefore, high time we included interindividual variability and revisited the drawing board of neurology and psychiatry.

Clinical presentations and mapping inter-individual differences are beginning to explain the observed variance in cognitive and behavioural measures. As such, a better understanding of variability is crucial to explain differences in human abilities and disabilities and improve our clinical models and predictions (Seghier & Price, 2018). While the cerebral white matter may not be a functional agent *per se* (see Innocenti et al. 2017; Rockland 2020 for discussion), it constrains the brain's functional organisation (Bouhali et al., 2014; Thiebaut de Schotten et al., 2017) and leads to cognitive impairment or complete loss of function when severed (Geschwind et al. 1965ab). Hence, mapping white matter variability may be an ideal surrogate measure to capture inter-individual differences 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 & Johansen-Berg, 2011). Tractography has widely been employed as a neuroimaging biomarker to link white matter phenotypes to cognition. In this instance, phenotypes are considered to be interindividual variation in white matter networks. Phenotypes are defined as the product of an environment-genotype interaction. White matter tracts, particularly language and limbic networks, have been shown to be sensitive to such interactions (Su et al., 2020; Budisaljevic et al., 2016; Budisaljevic et al., 2015). Consequently, white matter is subject to variations over the lifespan and changes resulting from training (Scholtz et al. 2009; Lebel et

al., 2019; Thiebaut de Schotten et al., 2014; 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. 2011; Howells et al. 2018) and clinical cohorts (*e.g.* Forkel et al., 2014; Forkel et al. 2020; Thompson 2017; Pacella et al. 2020). Therefore, tractography can be employed to study variability in the human brain and map functional white matter correlates.

Identifying consistent trends in tractography studies is crucial to map white matter phenotypes and their impact on cognition, hence a systematic review is timely. We mainly 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) measures of white matter pathways extracted from diffusion tractography. We concentrate on neuropsychological tests or clinical scales in healthy and pathological populations for behavioural measures. In this review, we summarise dimensional differences in structural connectivity in relation to cognition as a step towards the systematic inclusion of inter-individual variability in neuroscience studies.

Methods

We undertook a systematic review of published journal articles that correlated measures derived from white matter tractography with cognition or clinical symptoms, following PRISMA guidelines (Liberati et al., 2009). The resources obtained from this study and created for this data are made available as supplementary material: https://github.com/StephForkel/PhenotypesReview.git

Data Sources: A title/abstract search in MEDLINE and Scopus (which includes most of the EMBASE database, https://www.elsevier.com/solutions/embase-biomedical-research) was conducted. The search term ‘tractography’ returned a total of 5,303 in PubMed and 7,204 results in Scopus. We hence restricted our search (conducted on February 25th, 2020) to the following strings: (predictor OR "correlat*" OR regression OR “assoc*”) AND (tractography). Additional filters were applied to include only human adult studies published in English as final stage peer-reviewed articles in scientific journals. The search returned 1333 results on Pubmed and 2380 results on Scopus, yielding 3,713 records. There were no internal duplicates within each database, and we excluded 1224 external duplicates between the databases. After removing duplicates from these lists, a total of 2489 results were screened.

Data screening and eligibility: Figure 1 summarises the following workflow. During the screening, we applied further exclusion criteria leading to the exclusion of paediatric studies, non-human studies, pure methodological papers without behavioural correlates, correlations between tractography and physiological rather than behavioural measures (e.g. heart rate), non-brain studies (e.g. cranial nerves, spine, muscle), graph theory and tract-based spatial statistics (TBSS) studies, and case studies or mini-series (less than 10 participants/patients) and papers that reported no significant correlation. All studies reporting variability of white matter pathways using tractography that described a significant association with continuous cognitive measures, clinical symptom severity and/or continuous recovery were

included. After screening of the abstracts, we retained a list of 466 references. Full text screening further identified studies that fulfilled the exclusion criteria defined above. This led to a total of 326 studies included in the final analysis.

Study quality:

The QUADAS quality assessment tool (Whiting et al., 2003) was adapted for the review to document the steps taken by each paper to avoid bias and justify and validate the protocols. The following criteria were used to rate publications: 1) Sufficient detail provided to reproduce the protocol, 2) clearly defined white matter pathways, 3) the cohorts, cognitive measures or clinical characteristics were reported.

Data extraction: The following information was collected from the records: year of publication, cohort (e.g. healthy participants vs degeneration vs psychiatric vs neurological vs neurodevelopmental), sample sizes, left/right/unspecified hemisphere, tractography indices, label of white matter pathways, clinical symptoms, behaviour and/or cognitive domain, differential neuropsychological measures (*e.g.* Trail Making test), and finally the interaction between white matter pathways and neuropsychological assessments.

Data synthesis and analyses: In the present synthesis of this dataset, we summarised degeneration, neurosurgical and common neurological symptoms as a neurological group. Similarly, the psychiatric group included adult neurodevelopmental and psychiatric studies.

We also synthesised clinical symptoms, behaviour and/or cognitive domains using the following terms: We limited the cognitive domains taxonomy to the terms that are currently widely accepted in the literature, including attention, executive functions, language, memory, and reward. Terms defining behavioural domains included addiction, auditory, visual and motor behaviour, sleep, mood, social measures (*e.g.* theory of mind). To assess the sensitivity of tracts to clinical measures, we also included a “symptoms” dimension corresponding to neurological and psychiatric severity measures.

According to domains, the classification of the correlations was replicated three times by SJF, PF and HH and in case of disagreements, a consensus was reached. From these terms, we could extract variables of interest such as the number of correlations per tract (*i.e.* sensitivity or how likely a tract can correlate), but also the number of studies reporting significant correlations for that tract (*i.e.* popularity or how often studies report a significant correlation for that tract). Subsequently, we also investigated the number of correlations reported according to the domains of interest mentioned above (*i.e.* specificity to cognitive domains: attention, executive functions, language, memory, and reward; behavioural domains: addiction, auditory, visual and motor behaviour, sleep, mood, social; and symptoms severity).

Results

The number of correlations and studies per tract.

A total of 25 individual tracts were reported to correlate with performance on neuropsychological tests or clinical symptoms (Figure 2). Amongst these, certain pathways were more commonly correlated with cognitive-behavioural measures than others (Figure 2A). We report here the number of studies that described correlations (Figure 2A) and the number of correlations per tract (Figure 2B). Showing this difference is essential, as some studies reported more than one tract correlation. Notably, commonly 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 (Figure 2B).

Our review shows that most correlations and studies have been conducted in patients with neurological or psychiatric pathologies rather than controls (Figure 2). 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 fibres (Figure 3A). In the neurological groups, most correlations were described for the corticospinal tract, the corpus callosum, and the cingulum (Figure 3B). The cingulum, arcuate fasciculus, and uncinate fasciculus were the most commonly reported tracts to correlate with psychiatric symptoms (Figure 3C). 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 (Figure 3D). For the neurological group, the most studied tracts were also the most sensitive tracts, namely the corticospinal tract, corpus callosum, and cingulum (Figure 3E). In the psychiatric group, the most sensitive and popular pathways were the cingulum, arcuate fasciculus and uncinate (Figure 3F).

The number of correlations per domain. The analysis of domains and correlated pathways revealed that there was no one-to-one correspondence between one white matter tracts and one domain (Figure 4). The pathways with the clearest selectivity to one domain were the corticospinal tract for the motor domain and the cingulum for executive functions (Figure 4). Additional figures showing all correlations per domain for all tracts are available in the supplementary material (https://github.com/StephForkel/PhenotypesReview.git). This summary also shows that a tract's level of selectivity to one domain is often related to the tract's diversity of projections. For instance, the corpus callosum, which projects on most of the brain's surface (Karolis et al., 2019) is associated with most domains. Association tracts such as the arcuate fasciculus were also reported to be involved in several domains, but the most common association was with language measures. When separating the arcuate into its segments, this analysis showed that the long segment is mainly driving domain specificity of the arcuate with language. In contrast, the anterior and posterior segments of the arcuate fasciculus had a more substantial load on memory and attention (Figure 4).

Hemispheric specialisation. The analysis highlighted that the current body of literature is inconsistently specifying the studied hemisphere explicitly (Figure 5A). Amongst the 326 resources, a total of 674 significant tract-function correlations were reported. Within this data pool, an equal number 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. When looking at the distribution of

significant correlations with cognitive measures it was evident that the left hemisphere is more commonly studied (Figure 5A). Specifying the hemisphere for commissural tracts is of course not so relevant, however it certainly is when studying association or projection fibres, where providing information on hemisphere is essential, given what is known about functional lateralisation.

Diffusion indices. Various diffusion indices are used across the literature, including fractional anisotropy (FA), mean diffusivity (MD), number of streamlines, and voxels intersected by streamlines as a proxy of volume. These indices have been associated with microstructural properties and have been used to indicate axonal damage or degeneration (Beaulieu 2002; Ciccarelli et al., 2008; Afzali et al., 2021). Each index was extracted from the 326 studies and the results highlight that some measures are more commonly reported than others (Figure 5).

Discussion

Over the course of the last fifteen years, there have been over 300 studies in human adults showing significant correlations between white matter tracts and functions. These correlations lend support to the concept of the importance of inter-individual differences in healthy participants and across brain pathologies. Our systematic review highlights three main observations. The first is that tractography is a commonly used tool to study inter-individual variability and has proven to be a sensitive method in neurology, psychiatry, and healthy volunteers. Secondly, we observed a “tract bias” in the literature, by which we mean that the pathways that yield the highest number of significant correlations with behaviour are not necessarily those with the highest sensitivity for a specific cognitive function or 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.

Our investigation objectively collated tract-function correlations across neurological, psychiatric, and healthy populations. Most results were reported in pathological cohorts rather than in healthy participants (Figure 3). The predominance of pathological cohorts in correlational tractography may originate from the broader dispersion of the data points associated with pathologies. As the presence of pathology causes higher variability in both structure and function, this is more likely to be detected with a linear correlation. Another consideration may be that differences between healthy participants are commonly considered to be noise by most research teams (Kanai & Rees, 2011). 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 lateralisation). An alternative hypothesis could be that current neuroimaging or cognitive and behavioural tests are not sensitive enough to disentangle noise from real variability in healthy participants systematically. The latter may be improved by using finer-grained cognitive measures, higher resolution data, and better anatomical tract definitions.

Some pathways were more sensitive than others. Our review identified a total of 25 studied tracts that have been significantly correlated with cognitive measures or symptom severity in clinical cohorts and

healthy participants. The precise number of white matter tracts in the human brain remains unknown and variable estimates originate from the use of different methods. Most atlases suggest around 26 tracts can be reliably identified with most tractography methods (Mori, 2005; Lawes et al., 2008; Catani & Thiebaut de Schotten, 2008; Mori et al., 2009; Thiebaut de Schotten et al., 2011; Rojkova et al., 2016). Some recent atlases further identify additional intralobar connections (Catani et al., 2012; Guevara et al., 2012; Catani et al., 2017; Guevara et al., 2020). This review reported on some additional pathways that have not yet been incorporated into atlases, including the accumbofrontal tract and the vertical occipital fasciculus (Martínez-Molina et al. 2019; Rigoard et al., 2011, Vergani et al., 2016; Yeatman et al., 2013; Vergani et al., 2014). Our results also highlight a bias in the literature toward studying specific tracts that have very well-established functions (*e.g.* corticospinal tract, arcuate fasciculus) or are easy to dissect in clinical cohorts (*e.g.* cingulum). The omission of other tracts does, of course, not mean they are functionally irrelevant. It could be that they are as yet unstudied or show correlations with other non-routinely tested cognitive and behavioural measures. Some may have non-linear or indirect relationships with function, for which correlational approaches are not appropriate. Further, understudied pathways may be more challenging to reconstruct due to limited anatomical guidelines or available algorithms (*e.g.* U-shaped fibres, Attar et al., 2020, Mandelstam, 2012; Maffei et al., 2019a; 2019b).

For the most sensitive, or commonly correlated, tracts, several functions were reported. Even the corticospinal tract, although this was primarily studied within the motor domain (62.21% of correlations, Figure 4), showed a non-uniform functional profile. For instance, a few 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 support the idea of hierarchical brain organisation with some tracts involved in mediating many functions, whereas others may be more specific (Pandya and Yeterian 1990). While the number of associations is very likely to be biased by several 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 also showed that one pathway is relevant in multiple functions. Another possible interpretation of this finding is that human-ascribed definitions of white matter tracts are too coarse to be specific to only one given function. For example, segmenting the arcuate fasciculus into three components (Catani et al., 2005) showed correlations with more domain specificity than correlations with the entire arcuate fasciculus. This may call for finer-grained white matter divisions or data-driven approaches to identify segments of white matter that may be related to specific functions (see, for example, Foulon et al., 2018; Nozais et a., under review).

We also show differential patterns between healthy participants and pathological groups. One such example is the uncinate fasciculus that has been primarily associated with memory in healthy ageing (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 was implicated in learning new words in healthy participants (Lopez-Barroso et al., 2013), auditory hallucinations in schizophrenia

(Catani et al., 2011), and aphasia severity in stroke (Forkel et al., 2014). Therefore, the functions associated with a pathway might not purely be a product of the cortical regions the white matter connects to but instead relies on the interplay of one region with another. When pathology is introduced into this delicate network, for example by a lesion, differential patterns of symptoms may reflect the variable impact on brain regions within the network. 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).

There are tractography limitations that may have influenced the studies in the current work. We set out to systematically review tract-function correlations irrespective of these limitations, to identify broad patterns however it is essential to caveat this study by stating what tractography can and cannot do when interpreting results. While tractography has proven useful for research and clinical applications, interpretation of voxel-based indices' presents challenges (Dell'Acqua & 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*2mm, while the voxel sizes are often larger for clinical data leading to even lower spatial resolution. An $8mm^3$ 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 fibres and afflict tractography reconstructions with false positives and negatives. 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 partially correct for these distortions and disentangle some of these components and crossing fibres to extract tract-specific measurements (see Dell'Acqua & Tournier, 2019) however many of the studies here used the diffusion tensor rather than advanced HARDI or other methods. While recent research studies have methodological means to mitigate such distortions (*e.g.* Andersson et al., 2003), most current clinical studies still suffer from these limitations, potentially explaining the lack of tract-domain specificity.

Another source of inconsistencies originates from incoherent reporting of the anatomy. For example, 28% of records did not specify which hemisphere was studied or collapsed their white matter measures across both hemispheres and correlated this average with behaviour. Collapsing measurements from anatomical feature across both hemispheres might prove problematic for white matter pathways that are subject to more considerable inter-individual variability and might get over- and underrepresented in each hemisphere (*e.g.* Catani et al., 2007; Thiebaut de Schotten et al., 2011; Rojkova et al. 2016, Croxson et al., 2018; Howells 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 behaviour or disorder (Floris & Howells, 2018). Another limitation comes from inconsistencies in the classification of white matter pathways. For instance, the superior longitudinal fasciculus (SLF) was often considered in its entirety without specifying which branch was studied. When branches were specified, a variety of terminologies were used, including the three branches (SLFI-III,

Thiebaut de Schotten et al., 2011), or a lobar-based segmentation into a 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 fibres connecting frontal and parietal regions (*i.e.* "superior and longitudinal"; Thiebaut de Schotten et al., 2011) 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 fibre complex (Mars et al., 2016), inferior fronto-occipital fasciculus (Forkel et al., 2014), and inferior occipitofrontal fasciculus (Kier et al., 2004). The difference in terminology is owed mainly to the description of these pathways using different methods (Forkel et al., 2014) and some consensus is certainly needed to improve consistency in the literature (Maier-Hein et al., 2017; Mandonnet et al., 2018).

Additionally, to harvest the 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.* Ferreiera 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 may be more sensitive and specific than others, but some were underrepresented in our systematic review which prevented any valid comparison (Figure 5). Finally, while correlational research indicates that there may be a relationship between two variables (*e.g.* structure and function), it cannot assume causality and prove that one variable causes a change in another variable. This means that it is impossible to determine whether anatomical variability is driving behaviour or if the anatomy results from an expressed behaviour (*i.e.* the directionality problem) from this type of data. It is also not possible to know whether a third factor mediates the changes in both variables and that the two variables are in fact not related (*i.e.* the 'third variable problem'). Future studies using correlational tractography may benefit from exploring other statistical frameworks such as Bayesian methods to get closer to establishing causal relationships between variables (Pacella et al., 2019).

In conclusion, 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 help 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 towards more personalised approaches to medicine. With the improvements suggested in this systematic review, tract-function correlations could be a useful adjunct in studies predicting resilience and recovery in patients.

Declarations

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Supplementary material: https://github.com/StephForkel/PhenotypesReview.git

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Figures

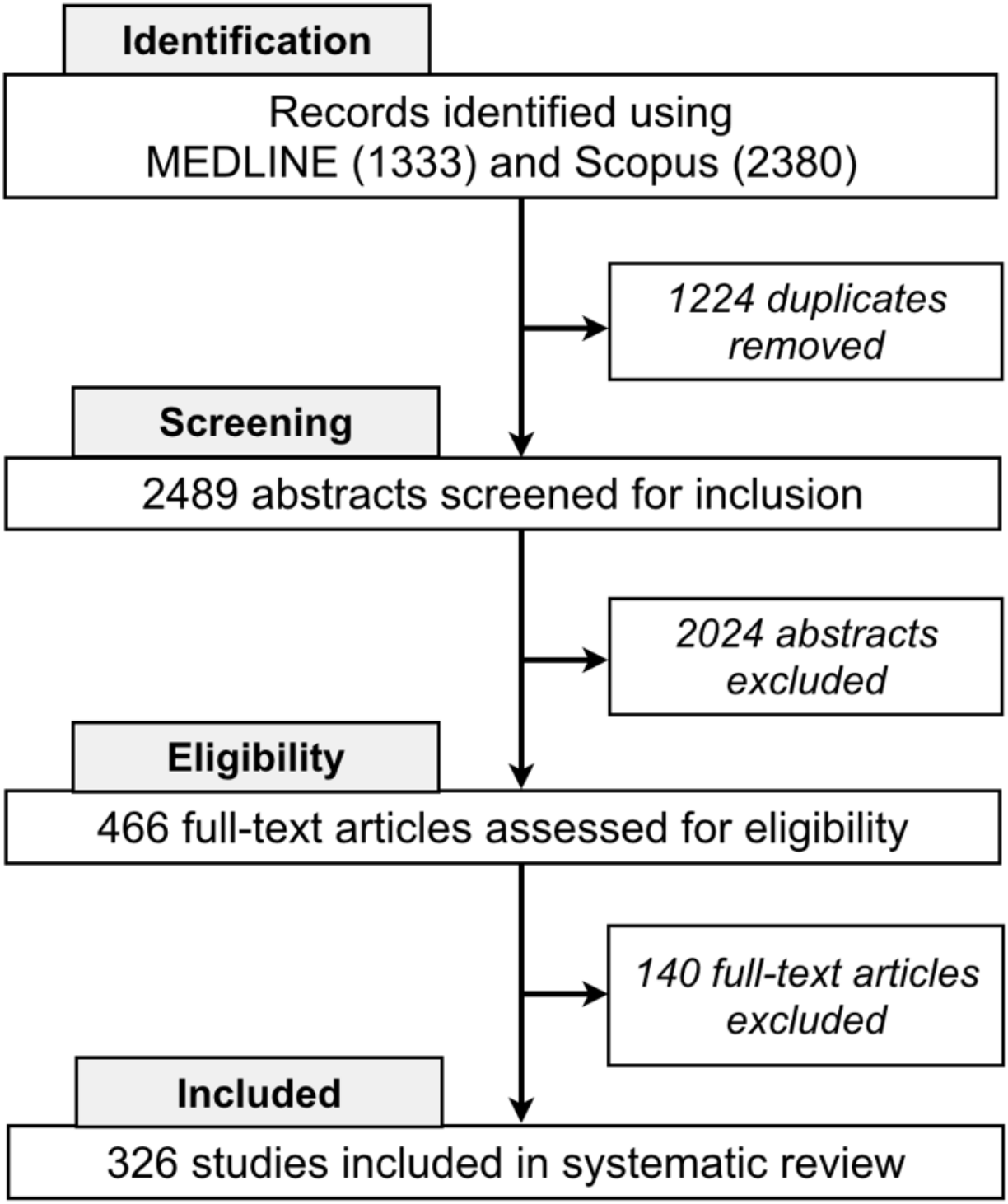

Figure 1

PRISMA flow chart.

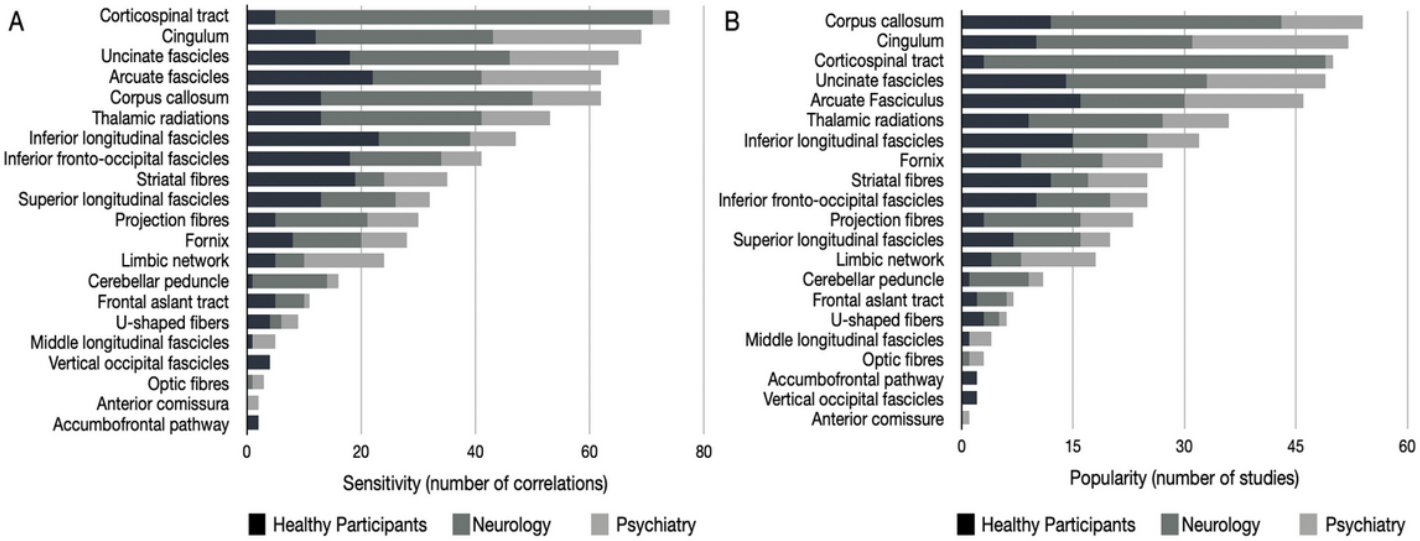

Figure 2

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 the number of studies represents tract popularity.

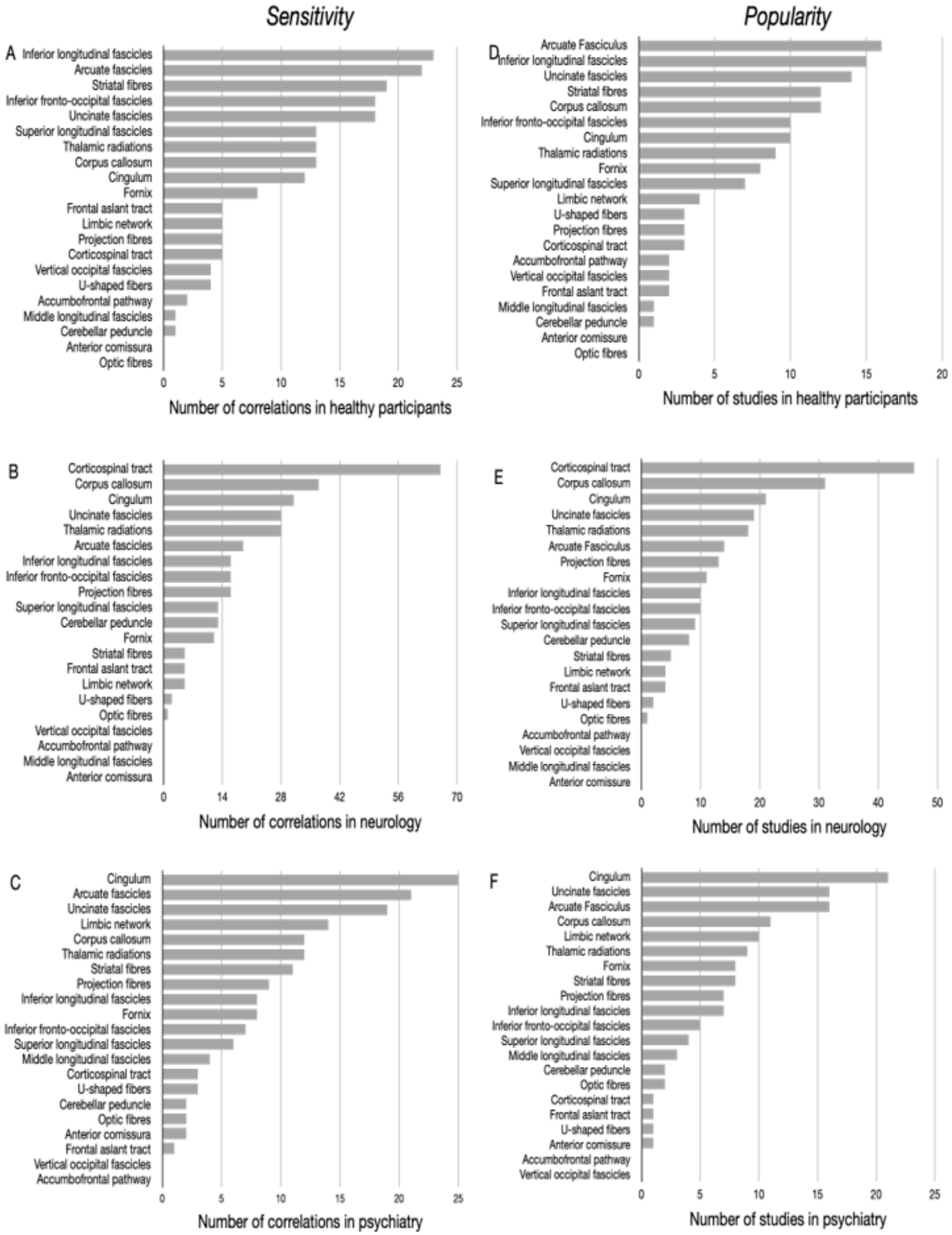

Figure 3

“Tract bias” in the literature. Tract sensitivity (A-C) and tract popularity (D-F) in healthy participants, neurology, and psychiatry. Number of correlations per tract is defined as sensitivity or how likely a tract can correlate and the number of studies reporting significant correlations for that tract is defined as popularity.

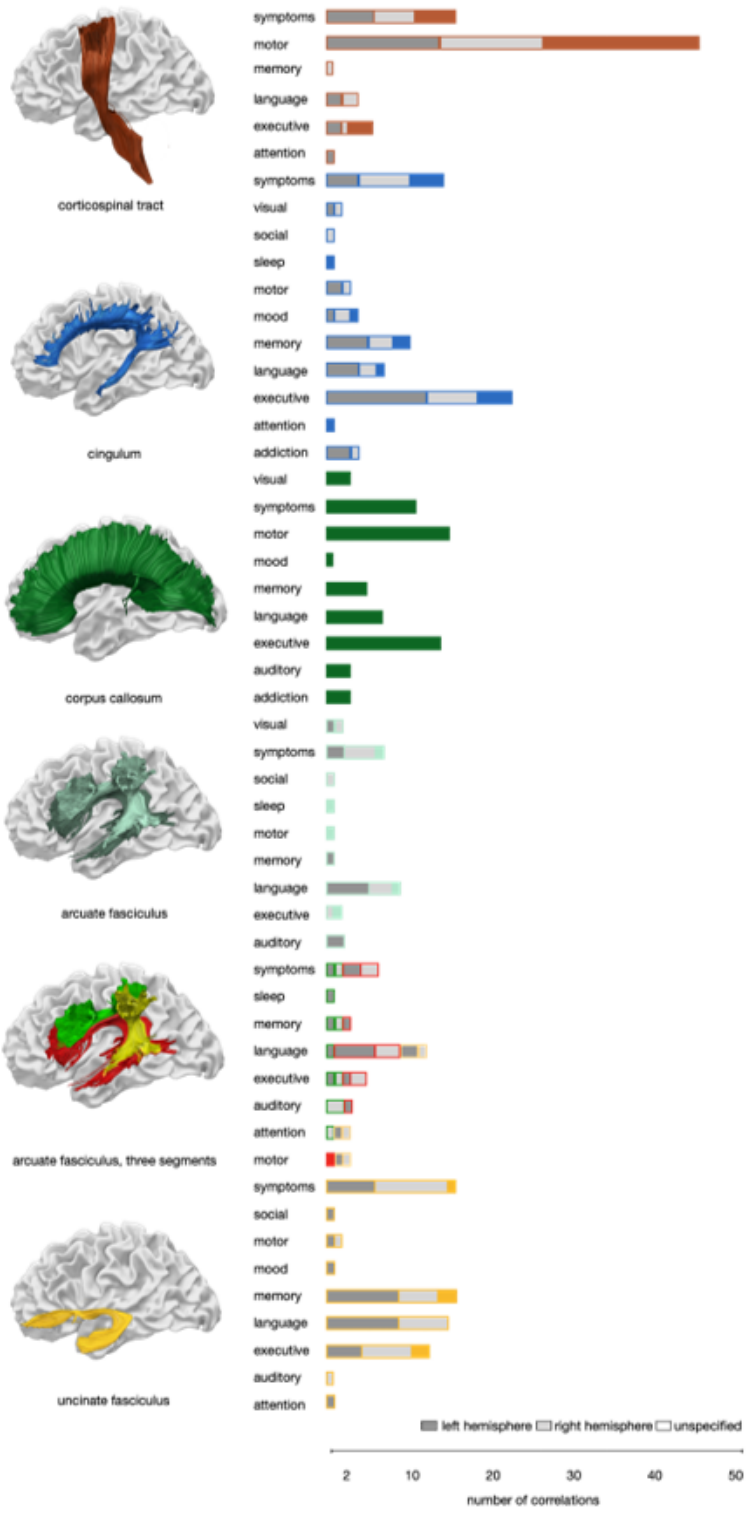

Figure 4

Tract domain specificity. The number of correlations between cognitive, behavioural or clinical assessments and white matter tracts demonstrates that the concept of ‘one tract-one function’ does not hold. The figure shows the most studied tracts as identified by the current study. The other tract-domain correlations are available as supplementary figures (see supplementary figures).

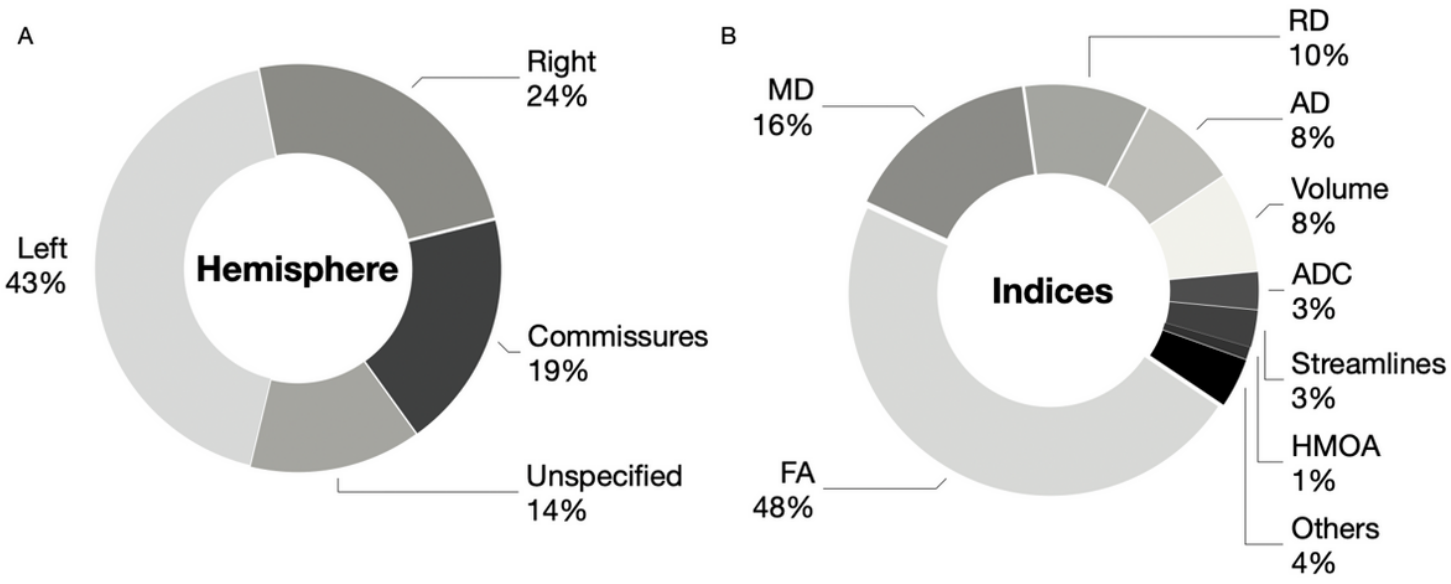

Figure 5

Summary of commonly reported hemisphere of the brain (A) and diffusion indices (B). The results indicate that tractography results in the left hemisphere are more often reported to correlate with cognitive-behavioural measures and that fractional anisotropy (FA) is the most commonly reported diffusion index. Mean diffusivity, MD; radial diffusivity, RD; axial diffusivity, AD; Apparent Diffusion Coefficient, ADC; Hindrance modulated orientational anisotropy, HMOA.