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Quantitative mapping of the brain's structural connectivity using diffusion MRI tractography: A review

Fan Zhang[a,*], **Alessandro Daducci**[b,1], **Yong He**[c,d,e,f,1], **Simona Schiavi**[b,1], **Caio Seguin**[g,h,1], **Robert E Smith**[i,j,1], **Chun-Hung Yeh**[k,l,1], **Tengda Zhao**[c,d,e,1], **Lauren J. O'Donnell**[a,*]

[a]Brigham and Women's Hospital, Harvard Medical School, Boston, USA

[b]Department of Computer Science, University of Verona, Verona, Italy

[c]State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China

[d]Beijing Key Laboratory of Brain Imaging and Connectomics, Beijing Normal University, Beijing, China

[e]IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, China

[f]Chinese Institute for Brain Research, Beijing, China

[g]Melbourne Neuropsychiatry Centre, University of Melbourne and Melbourne Health, Melbourne, Australia

[h]The University of Sydney, School of Biomedical Engineering, Sydney, Australia

[i]The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

[j]Florey Department of Neuroscience and Mental Health, The University of Melbourne, Melbourne, Australia

[k]Institute for Radiological Research, Chang Gung University, Taoyuan, Taiwan

[l]Department of Psychiatry, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan

Abstract

Diffusion magnetic resonance imaging (dMRI) tractography is an advanced imaging technique that enables *in vivo* reconstruction of the brain's white matter connections at macro scale. It provides an important tool for quantitative mapping of the brain's structural connectivity using measures of connectivity or tissue microstructure. Over the last two decades, the study of

*Corresponding authors. fzhang@bwh.harvard.edu (F. Zhang), odonnell@bwh.harvard.edu (L.J. O'Donnell).
[1]All middle authors have contributed equally to this work.

Credit Author Statement

Fan Zhang: Conceptualization, Project administration, Visualization, Writing – original draft, Writing – review & editing. Alessandro Daducci: Conceptualization, Writing – original draft, Writing – review & editing. Yong He: Conceptualization, Writing – original draft, Writing – review & editing. Simona Schiavi: Conceptualization, Writing – original draft, Writing – review & editing. Caio Seguin: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. Robert Smith: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. Chun-Hung Yeh: Conceptualization, Writing – original draft, Writing – review & editing. Tengda Zhao: Conceptualization, Writing – original draft, Writing – review & editing. Lauren J. O'Donnell: Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

brain connectivity using dMRI tractography has played a prominent role in the neuroimaging research landscape. In this paper, we provide a high-level overview of how tractography is used to enable quantitative analysis of the brain's structural connectivity in health and disease. We focus on two types of quantitative analyses of tractography, including: 1) *tract-specific analysis* that refers to research that is typically hypothesis-driven and studies particular anatomical fiber tracts, and 2) *connectome-based analysis* that refers to research that is more data-driven and generally studies the structural connectivity of the entire brain. We first provide a review of methodology involved in three main processing steps that are common across most approaches for quantitative analysis of tractography, including methods for tractography *correction, segmentation* and *quantification*. For each step, we aim to describe methodological choices, their popularity, and potential pros and cons. We then review studies that have used quantitative tractography approaches to study the brain's white matter, focusing on applications in neurodevelopment, aging, neurological disorders, mental disorders, and neurosurgery. We conclude that, while there have been considerable advancements in methodological technologies and breadth of applications, there nevertheless remains no consensus about the "best" methodology in quantitative analysis of tractography, and researchers should remain cautious when interpreting results in research and clinical applications.

1. Introduction

Diffusion magnetic resonance imaging (dMRI) tractography is an imaging method that uniquely enables *in vivo* reconstruction of the brain's white matter connections at macro scale (Basser et al., 2000). Since the first dMRI tractography methods were proposed in 1998–2000 (Basser, 1998; Basser et al., 2000; Conturo et al., 1999; Mori et al., 1999; Westin et al., 1999), tractography has enabled mapping of the brain's structural connectivity in many neurological applications such as aging, development and disease (Assaf and Pasternak, 2008; Ciccarelli et al., 2008; Essayed et al., 2017; Nucifora et al., 2007; Shi and Toga, 2017; Yamada et al., 2009). Initial applications of tractography enabled the visualization of white matter tracts, a primarily qualitative approach that remains highly relevant today both in the clinic (Abhinav et al., 2015; Essayed et al., 2017; Pujol et al., 2015) and for the study of neuroanatomy (Catani et al., 2002; Ciccarelli et al., 2003; Makris et al., 2005). Recently, quantitative approaches have become popular tools for studying the brains connectivity and tissue microstructure using tractography. In this paper, we provide a high-level overview of how tractography is used to enable *quantitative* analysis of the brain's structural connectivity. This review is intended to be useful to researchers studying the white matter, developers of quantitative analysis methods, and clinicians interpreting results related to tractography.

Due to the large number of proposed quantitative approaches and the evolution of the field over two decades, there is a proliferation of terminology related to the quantitative analysis of dMRI tractography. Therefore, we begin with a listing of common terms used throughout this paper and their definitions, as provided in Table 1. We also provide a visualization of many key concepts that will be used in the paper (Fig. 1).

Many quantitative tractography approaches can be applied to study the brain's structural connectivity in health and disease. The fundamental goal of these analyses is to estimate quantitative measures of connectivity (or microstructure) of some pathway (or pathways) of interest. Quantitative analyses of tractography can be categorized into two main categories or styles: *tract-specific* analyses and *connectome-based* analyses (this categorization is helpful but imperfect, as some approaches blend aspects of both analysis styles). Tract-specific analysis refers to research that is typically hypothesis-driven and studies particular anatomical fiber tracts (Alexander et al., 2007; Levitt et al., 2020; Shany et al., 2017; Yeo et al., 2014). Tract-specific analysis has been increasingly adopted, particularly for the study of local white matter regions in health and disease (Alexander et al., 2007; Shany et al., 2017; Yeo et al., 2014). Connectome-based analysis refers to research that is more data-driven and generally studies the structural connectivity of the entire brain (Bastiani et al., 2012; Ingalhalikar et al., 2014; Sporns et al., 2005; Zalesky et al., 2012). This type of analysis aims to understand patterns of whole-brain anatomical connectivity, and therefore relies on tractography performed across the entire white matter.

In this paper, we first provide a brief introduction to tractography (Section 2), then a review of methodology for quantitative tractography analysis (Sections 3–5), followed by a review of studies that use quantitative tractography analysis to study the brain in health and disease (Section 6). For the methodology review, we organize the paper according to three main processing steps that are common across most approaches for quantitative analysis of tractography. The first common step corrects potential biases in tractography reconstruction that may otherwise be detrimental to, or outright preclude, quantitative analysis of such data; we refer to this as tractography *correction* (Section 3). The second common processing step identifies white matter pathways (e.g., subdivisions of the tractogram) that are meaningful for quantification of brain connectivity; we refer to this as tractography *segmentation* (Section 4). The third common step extracts quantitative indices that describe the microstructure and/or the "strength" of the brain connections; we refer to this as tractography *quantification* (Section 5). In each section, we aim to describe methodological choices, their popularity, and their potential pros and cons. Finally, we review studies that have used quantitative tractography approaches to study the brain's white matter, including applications in development, aging, neurological disorders, mental disorders, and neurosurgery (Section 6).

2. Brief introduction to tractography

"Tractography" can refer to any computational process that estimates the anatomical trajectories of white matter fiber pathways from dMRI data. There are many methods available to perform tractography, including traditional streamline tractography based on the diffusion tensor model (Basser et al., 2000; Basser and Pierpaoli, 1996), which was originally proposed (as "hyperstreamlines") for the visualization of tensor fields in the computer graphics community in 1993 (Delmarcelle and Hesselink, 1993). More recently, many streamline tractography methods using advanced diffusion models have been proposed and are under active development (Behrens et al., 2007; Descoteaux et al., 2008; Feng and He, 2020; Fernandez-Miranda et al., 2012; Friman et al., 2006; Jackowski et al., 2005; Jeurissen et al., 2014; Lazar and Alexander, 2005; Malcolm et al., 2010; Reddy

and Rathi, 2016; Tournier et al., 2010; 2003; Wasserthal et al., 2019). Furthermore, many alternative tractography algorithms have been proposed, such as front evolution (Pichon et al., 2005; Sepasian et al., 2012; Tournier et al., 2003), geodesic (identifying likely connection trajectories based on assumed endpoints) (Jbabdi et al., 2008; 2007; Li et al., 2014; O'Donnell et al., 2002; Schreiber et al., 2014; Wu et al., 2009), atlas-based (Wasserthal et al., 2019; Yendiki et al., 2011), differential tractography (Yeh et al., 2019b) and various forms of "global" tractography that simultaneously fit the entire tractography reconstruction to all image data (either by progressively forming linked chains from a large set of randomly-initialized short segments (Christiaens et al., 2015; Fillard et al., 2009; Kreher et al., 2008; Mangin et al., 2013; Mangin et al., 2002; Reisert et al., 2011; Teillac et al., 2017)or iteratively perturbing a set of candidate trajectories (Battocchio et al., 2020; Close et al., 2015; Lemkaddem et al., 2014; Wu et al., 2012b). Work is additionally underway to improve tractography using machine learning (Neher et al., 2017; Poulin et al., 2019; Sarwar et al., 2020; Wasserthal et al., 2019; Wegmayr et al., 2018).

While a detailed introduction of tractography methods is out of the scope of this review, we refer the readers to these review papers (Jeurissen et al., 2019; Neher et al., 2015; Rheault et al., 2020b; Smith et al., 2020c) that are specific to tractography algorithms.

Many software packages are available to perform tractography research, including ANIMA (Descoteaux et al., 2008), BrainSUITE (Shattuck and Leahy, 2002), Camino (Cook et al., 2006), COMMIT (Daducci et al., 2013; 2014; Ocampo-Pineda et al., 2021; Schiavi et al., 2020a), Diffusion toolkit (Wang et al., 2007), Dipy (Garyfallidis et al., 2014), DMIPY (Fick et al., 2019), DSI studio (Yeh et al., 2013), DTIstudio (Jiang et al., 2006), ExploreDTI (Leemans et al., 2009), Fiber-Navigator (Chamberland et al., 2014), FSL (Jenkinson et al., 2012), MITK (Wolf et al., 2005), MRtrix3 (Tournier et al., 2012; 2019), PANDA (Cui et al., 2013), SlicerDMRI (Norton et al., 2017; Zhang et al., 2020b), TractSeg (Wasserthal et al., 2018), and Tracula (Yendiki et al., 2011). It is important to note that tractography is known to be sensitive to the choice of the underlying fiber tracking algorithms, which can further affect any subsequent quantitative analyses using the tractography data. On one hand, tractography results may vary across the large set of available diffusion models (Afzali et al., 2020; Alexander, 2006; Panagiotaki et al., 2012; Yablonskiy and Sukstanskii, 2010) and tractography methods (Basser et al., 2000; Behrens et al., 2007; Descoteaux et al., 2008; Feng and He, 2020; Fernandez-Miranda et al., 2012; Friman et al., 2006; Jackowski et al., 2005; Jeurissen et al., 2014; Lazar and Alexander, 2005; Malcolm et al., 2010; Reddy and Rathi, 2016; Tournier et al., 2010; 2003; Wasserthal et al., 2019). On the other hand, tractography results can also be sensitive to the choice of parameters (such as seeding and stopping thresholds) within a certain algorithm (Chamberland et al., 2014; Côté et al., 2013; Gong et al., 2018; Moldrich et al., 2010; Xie et al., 2020). While many research studies have been performed to compare different tractography algorithms (Bastiani et al., 2012; Fillard et al., 2011; Petrov et al., 2017; Pujol et al., 2015; Sinke et al., 2018; Wilkins et al., 2015; Zhan et al., 2015), there is no consensus on "the best algorithm."

3. Improving tractography quality: methods for tractography correction

The goal of tractography correction methods is to tackle potential biases and errors that are produced in conventional or raw tractography algorithms. Where such an issue can be clearly demonstrated in exemplar data, and a tailored mechanism proposed that intrinsically addresses the issue, it is expected that the employment of such a mechanism in the reconstruction of empirical image data will lead to overall improved biological accuracy of the reconstruction (even in the absence of direct validation of such), which is important for the extraction of anatomical fiber tracts (Section 4.1) and the construction of quantitative structural connectivity matrices (Section 5.5). In this section, we consider the near-ubiquitous "streamlines" paradigm for dMRI tractography (Basser, 1998; Basser et al., 2000; Behrens et al., 2007; Conturo et al., 1999; Descoteaux et al., 2008; Feng and He, 2020; Fernandez-Miranda et al., 2012; Friman et al., 2006; Jackowski et al., 2005; Lazar and Alexander, 2005; Malcolm et al., 2010; Mori et al., 1999; Reddy and Rathi, 2016; Tournier et al., 2010; 2003; Wasserthal et al., 2019; Westin et al., 1999), and the ways in which specific undesirable behaviors or biases may be ameliorated through specific targeted mechanisms; see Fig. 2 for a visual summary of the relevant tractography biases included.

3.1. Curvature overshoot bias

Possibly the earliest bias established for dMRI tractography was the fact that if the streamline algorithm simply takes a step of finite size in the direction of the local fiber orientation at the current vertex (a so-called "first-order" method), streamlines in curved bundles will tend to under-estimate the curvature, resulting in erroneous trajectories (Tournier et al., 2002). While use of a step size that is small relative to the image voxel size mitigates the issue, use of a higher-order integration method during tracking that directly accounts for such curvature is a more direct solution (Basser et al., 2000). However, doing so in a manner that is compatible with diffusion models that account for crossing fibers can be technically difficult (Aydogan and Shi, 2020; Cherifi et al., 2018; Tournier et al., 2010).

3.2. Termination bias

"Termination" refers to the location at which the propagation of a streamline is ceased. Just as a tractography algorithm should produce streamlines whose tangents are faithful to the underlying fiber orientations, those streamlines should also terminate at locations corresponding to the endpoints of the underlying fiber tracts. Biases or inadequacies in such can result in partial fiber streamlines that stop prematurely in the white matter — despite the fact that white matter fibers synapse in the gray matter (Daducci et al., 2016) — or even that enter fluid-filled regions or cross sulcal banks. Such issues can be prevalent as tractography algorithms often operate using only the fitted diffusion model (e.g., diffusion tensor (Basser and Pierpaoli, 1996) or constrained spherical deconvolution (CSD) (Jeurissen et al., 2014; Tournier et al., 2007) in each image voxel. While these models provide strong evidence regarding fiber *orientations* to inform the direction of streamline propagation, the evidence they provide regarding where such fibers *stop* (and hence where streamlines should ideally be terminated) is weak (indeed, the diffusion-weighted signal itself does not provide direct evidence of fiber terminations (Smith et al., 2020b). Most fiber tracking algorithms exploit heuristic thresholds on features such as diffusion model anisotropy and streamlines curvature

to serve as tractography termination criteria. However, the indirect nature of these metrics for this task, combined with the inferior spatial resolution of diffusion-weighted imaging, leads to such errors being highly prevalent (Smith et al., 2012). These common termination criteria are therefore not adequate to ensure biologically plausible streamline generation, resulting in a substantial proportion of streamlines from whole-brain tractography being unreasonable for quantification of white matter fiber connectivity (Yeh et al., 2016a).

The ill-posed nature of streamline terminations can be addressed by utilizing anatomical reference data to impose relevant prior information. This can ensure that the reconstructed streamlines fulfill some fundamental assumptions we could make, given an a priori understanding of how neurons are organized in the brain. For instance, axons emanate from cell bodies within the gray matter and connect to other cells elsewhere in either the brain or body, but they do not synapse in the middle of white matter or propagate into ventricles. Unlike conventional tractography algorithms, in which termination points can be distributed almost anywhere in the brain, the Anatomically-Constrained Tractography (ACT) framework (Smith et al., 2012) and similar methods (Girard and Descoteaux, 2012; Lemkaddem et al., 2014; Yeh et al., 2017) ensure that both streamline propagation and termination are constrained based on knowledge of where neuronal fibers locate, e.g., connecting between gray matter areas via the white matter. Although these methods cannot guarantee that every streamline accurately traces the complete trajectory of an underlying fiber connection, they do prevent the generation of streamlines that *cannot possibly* represent biological connectivity within the brain.

3.3. Connection density biases

While streamline tractography provides estimates of structural connection trajectories that are consistent with the underlying fiber orientations, it does not provide any guarantees regarding consistency between the *number* of such reconstructed connections with the density of those underlying fibers (i.e., the actual number of axons in a white matter region) (Jones, 2010; Jones et al., 2013). This limitation is often expressed as the mantra “streamline count is not quantitative.” There are myriad factors that may modulate the empirical streamline count between pathways, or within a pathway across individuals. Many are emergent phenomena from the nuances of the operation of any particular streamlines algorithm and therefore difficult to characterise. Nevertheless, the fact it can be trivially demonstrated that both that streamline count can be erroneously modulated in the absence of a difference in connection strength and erroneously constant in the presence of a difference in connection strength (Figs. 2, 3) highlights the inappropriateness of applying such a strong biological interpretation to raw streamline count.

What would give greater confidence to the interpretation of tractography-based connection density as a quantitative measure is if, throughout the white matter, there were correspondence between the local density of reconstructed connections and the local density of fibers as evidenced by the diffusion image data (Smith et al., 2020a). Initially, aspiration for achieving this was limited to “global” tractography algorithms as mentioned in Section 2. More recently, methods have been devised to address this task by instead utilizing a pre-generated whole-brain streamline tractogram and modulating the contribution of each

streamline toward the reconstructed white matter fiber density. Initial methods achieved this by selecting a subset of streamlines that best fit the diffusion image data, i.e., BlueMatter (Sherbondy et al., 2009), MicroTrack (Sherbondy et al., 2010) and SIFT (Smith et al., 2013), while later methods estimate a multiplier to be applied to each streamline, i.e., COMMIT (Daducci et al., 2013; 2014), LiFE (Pestilli et al., 2014), SIFT2 (Smith et al., 2015b), COMMIT2 (Schiavi et al., 2020a) and $\text{COMMIT2}_{\text{tree}}$ (Ocampo-Pineda et al., 2021); these "weights" represent an effective cross-sectional area of each streamline, which can be utilized as a direct measure of connection density (Smith et al., 2020a) (or indeed to modulate streamline contributions toward other aggregate measures of the connectivity "strength"; see Section 5).

3.4. Gyral bias

Gyral bias in tractography is the bias towards generating streamlines that terminate in gyri rather than sulci (Schilling et al., 2018a; Wu et al., 2020b), which reduces the agreement of the initiations or terminations of fiber streamlines with known ground truth from tracer studies and histology (Aydogan et al., 2018; Budde and Annese, 2013). The source of the gyral bias is multifactorial, such as the complexity of axon arrangement at the junction of cortical grey matter and superficial white matter (Van Essen et al., 2014). The partial volume effect from the limited MRI spatial resolution introduces difficulties in distinguishing complex fiber configurations based on the reconstructed fiber orientation distributions (FODs). Increasing the image resolution is beneficial to mitigate the gyral bias (Heidemann et al., 2012; Sotiropoulos et al., 2016), but is constrained by the signal-to-noise ratio of the acquired dMRI data. Even operating on high-resolution dMRI data, current tractography algorithms have been shown to deviate from the ground-truth fiber projections derived from histological staining, with greater streamline densities at gyral crowns than sulcal banks (Schilling et al., 2018b). The complex folding and convolutions of cortical gyri also pose challenges for the reconstruction of long-range connections (Reveley et al., 2015).

A surface flow approach has been proposed to model the arrangement of superficial axonal fibers at gyral crowns, thereby improving the consistency between streamlines' initiations or terminations and the expectations from histological data (St-Onge et al., 2018). More recently, the gyral bias has been shown to be alleviated using an asymmetric FOD technique (Wu et al., 2020c), which can depict the highly-curved fiber geometry appearing at the superficial white matter (Bastiani et al., 2017; Wu et al., 2020c).

3.5. False positive connections

Several orders of magnitude separate the resolution of dMRI acquisitions (cubic millimeters) from the typical size of the axons (few micrometers). This discrepancy introduces ambiguities in the white matter that can be compatible with multiple streamline configurations and are *difficult for tractography to resolve* (Girard et al., 2020; Guevara et al., 2012; Maier-Hein et al., 2017). This ill-posed nature of tractography has received a renewed interest in the past few years, and several studies have raised serious concerns about the anatomical accuracy of the reconstructions (Maier-Hein et al., 2017; Thomas et al., 2014). In particular, it has been shown that tractography techniques suffer from a large number of false positives, i.e., streamlines that are reconstructed but do not correspond

to real anatomical bundles, and that these erroneous connections can severely bias the estimation of connectivity (Drakesmith et al., 2015; Maier-Hein et al., 2017; Zalesky et al., 2016b). The anatomical accuracy of the reconstructions can be improved by *manually filtering the streamlines* with inclusion/exclusion ROIs, as seen in Section 4.1, but this requires prior knowledge of "where white matter pathways start, where they end, and where they do not go" (Schilling et al., 2020a). However, more automated procedures are desirable especially when analyzing large cohorts of subjects.

A widely-used approach to attempt to alleviate false positive connections when building a structural connectivity matrix is *thresholding* (Fornito et al., 2016), which refers to the removal of edges whose strength is smaller than a certain cut-off value. This strategy implicitly assumes a correlation between the strength of a reconstructed edge and its validity, which can be violated in a range of ways due to the errors produced by streamlines tractography not being simply random variance. The capacity for thresholding to differentiate between true and spurious connections remains a debated topic in the field.

Alternative solutions have been proposed, which are *either knowledge- or data-driven*. The former are described in Section 4.1, and typically use fully- or semi-automated algorithms, e.g., clustering, as a means to detect and discard streamlines considered outliers based on anatomical priors or geometrical properties, e.g., length and shape. On the other hand, the methods described in Section 3.3 for addressing density biases can also be used as filtering procedures, in which the streamlines that are not supported by the acquired dMRI data, i.e., whose estimated weight is zero, are discarded. While these approaches achieve good results in terms of removing duplicate streamlines or isolated ones that are likely spurious, actually none proved effective in discriminating between true and spurious connections in the connectome networks (Maier-Hein et al., 2017; Schiavi et al., 2020a).

It was recently demonstrated that the performance of filtering methods can be significantly boosted by *combining knowledge- and data-driven strategies*. These new formulations (Ocampo-Pineda et al., 2021; Schiavi et al., 2020a) allow taking explicitly into account two fundamental assumptions about the connections in the brain: (i) fibers are naturally organized in bundles (Mandonnet et al., 2018; Udin and Fawcett, 1988), and (ii) the number of bundles should be low to minimize the overall wiring cost (Bullmore and Sporns, 2012). This prior knowledge helps resolve some of the ambiguities present in the data and, as a consequence, allows significant improvement of the anatomical accuracy of the connectome (Ocampo-Pineda et al., 2021; Schiavi et al., 2020a). This is achieved by organizing the streamlines into groups and seeking for solutions which explain the measured signal with the minimum number of bundles, using the Group Lasso regularization (Yuan and Lin, 2006), thus promoting sparsity in the space of connections, rather than in the space of individual streamlines as implicitly done in previous filtering methods.

Research is still underway to determine the best method(s) for filtering, with some disagreement on the beneficial versus detrimental effect of these methods on the structural connectome (Buchanan et al., 2020; Civier et al., 2019; Drakesmith et al., 2015; Frigo et al., 2020; Schiavi et al., 2020a; Yeh et al., 2016a).

4. Defining regions for quantitation: methods for tractography segmentation

The goal of white matter tractography segmentation is to identify white matter pathways (e.g., subdivisions of the tractogram) that are meaningful for quantification of the brain's structural connectivity. Critically, this step enables cross-subject quantitative comparison of the segmented white matter pathways; see (Smith et al., 2014) for a review of general considerations in multi-subject dMRI studies. (Tractography segmentation is also critical for qualitative applications such as visualization of fiber tracts, e.g., for neurosurgical white matter mapping; see Section 6.4.) Tractography segmentation methods can be generally grouped into two categories, related to the tract-specific and connectome-based analysis approaches, as illustrated in Fig. 3. The first category of methods identify anatomical white matter fiber tracts and label them with traditional names (such as the arcuate fasciculus or the corticospinal tract) (Section 4.1). The second category of methods parcellate, or subdivide, the entire white matter into many white matter parcels based on information about the streamline trajectories and/or endpoints (Section 4.2).

4.1. Anatomical tract identification

Anatomical tract identification aims to identify tractography streamlines that correspond to anatomically named white matter fiber tracts. This task is non-trivial, given the complex structures of the white matter anatomy and the large number of streamlines in the tractogram.

Conventional anatomical tract identification methods rely on *manual streamline selection*, also referred to as *virtual dissection*, where experts in anatomy interactively select tractography streamlines using manually drawn ROIs in the brain (Catani et al., 2002; de Schotten et al., 2011; Stieltjes et al., 2001; Wakana et al., 2007). Usually, inclusion ROIs are placed in the gray matter (cortical and subcortical) to define where the streamlines should terminate and in the white matter to define where the streamlines should pass, and exclusion ROIs are placed in other regions to exclude undesired streamlines (Rheault et al., 2020a; Wakana et al., 2007). Manual streamline selection is considered to be the gold standard to delineate anatomical fiber tracts in tractography and has been widely used to validate other anatomical tract identification techniques (Poulin et al., 2019; Pujol et al., 2015; Xie et al., 2020). Manual selection is also used in studies where specific clinical expertise is needed, e.g., for presurgical white matter mapping in tumor patients where the tumor and lesion can largely displace white matter fiber tracts (Radmanesh et al., 2015).

Due to the fact that manual tract selection is time-consuming and has high clinical and expert labor costs, modern studies increasingly focus on automated tract identification methods. These methods can be categorized into three categories: *ROI-based, streamline labeling*, and *direct segmentation*.

The *ROI-based* methods are the most commonly used. They automate ROI computation and perform streamline selection based on the ROIs a streamline terminates in and/or passes through. The majority of the ROI-based methods leverage a brain ROI atlas and use an

image registration to automatically align the ROIs in the atlas space to the subject space (Allan et al., 2020; Astolfi et al., 2020; Hua et al., 2008; Lawes et al., 2008; Schurr et al., 2019; Verhoeven et al., 2010; Wassermann et al., 2016; Yeatman et al., 2012; Zhang et al., 2008; 2010). Currently, popularly used brain ROI atlases include those provided in Freesurfer (Desikan et al., 2006; Fischl, 2012), MNI–ICBM152 (Mazziotta et al., 2001; Mori et al., 2008; Oishi et al., 2009; 2008), and JHU-DTI (Wakana et al., 2007; 2004) (see (Hansen et al., 2020) for a review of more atlases). There are also ROI-based methods that directly predict ROIs in subject space using machine learning (Astolfi et al., 2020; Li et al., 2020b).

The second category of automated tract identification methods, *streamline labeling*, assigns an anatomical label to each individual streamline. Often, streamline labeling is done by computing the geometric distance of each streamline to labeled streamlines in a reference tract segmentation, and then assigning a streamline label based on the closest reference tract (Bertò et al., 2020; Clayden et al., 2007; Gupta et al., 2018; 2017b; Kumar et al., 2019; Labra et al., 2017; Lam et al., 2018; Liu et al., 2019; Maddah et al., 2005; Xu et al., 2019; Yang et al., 2020; Zhang et al., 2020a). There are also learning-based segmentation approaches that train a model from the reference tract segmentation data and predict an anatomical label for each streamline in a new subject (Gupta et al., 2018; 2017b; Kumar et al., 2019; Lam et al., 2018; Liu et al., 2019; Xu et al., 2019; Yang et al., 2020; Zhang et al., 2020a). To reduce the amount of labeling for each streamline, many streamline labeling methods first group streamlines into clusters (known as fiber clustering), followed by assigning an anatomical label for each cluster, thus labeling each streamline (Avila et al., 2019; Chekir et al., 2014; Garyfallidis et al., 2018; Guevara et al., 2012; Li et al., 2010; O'Donnell and Westin, 2007; Román et al., 2017; Ros et al., 2013; Siless et al., 2018; 2020; Tunç et al., 2014; Vázquez et al., 2020; Wu et al., 2020a; Yeh et al., 2018; Yoo et al., 2015; Zhang et al., 2018c; Ziyan et al., 2009).

The third category of automated tract identification is called *direct segmentation* in the literature (Bazin et al., 2011; Dong et al., 2019; Eckstein et al., 2009; Li et al., 2020a; Lu et al., 2020; Ratnarajah and Qiu, 2014; Reisert et al., 2018; Rheault et al., 2019; Wasserthal et al., 2018; 2019; Yendiki et al., 2011; Zöllei et al., 2019). Unlike the aforementioned methods that work on precomputed tractography streamline data, the *direct segmentation* methods operate on DWI data (Yendiki et al., 2011; Zöllei et al., 2019) or derived volumetric image data (e.g., FOD maps (Wasserthal et al., 2018) and streamline density maps (Lu et al., 2020)) to predict the location for multiple tracts of interest, followed by performing tractography for only these tracts. Although the direct segmentation methods are relatively new and are relatively less used than the ROI-based and streamline labeling methods, the success of methods such as TRACULA (Yendiki et al., 2011), Tract-Seg (Wasserthal et al., 2018) and Bundle-specific tractography (BST) (Rheault et al., 2019) has shown highly promising tract segmentation performance.

There are several points that should be considered when selecting a method for anatomical tract identification. First, given the fact that there is no ground truth in tractography, validation of a tract identification method is difficult. One commonly used strategy to assess a tract identification method is to evaluate its reproducibility (in terms of intra-

and inter-rater as well as test-retest reproducibility) (Rheault et al., 2020a; Tong et al., 2019; Zhang et al., 2019). Methods using manual streamline selection have been shown to be highly reproducible for specific tracts and segmentation protocols using the diffusion tensor tractography (Wakana et al., 2007), but with more modern multi-fiber tractography, reproducibility is lower, potentially due to the increase in spurious streamlines (Rheault et al., 2020a). However, manual streamline selection is still considered to be the gold standard for benchmarked comparisons and algorithm training (Kreilkamp et al., 2019; Wasserthal et al., 2018; Zhang et al., 2010). For automated tract identification, one study indicates that streamline labeling has higher test-retest reproducibility than ROI-based segmentation (Zhang et al., 2019); however, no consensus has been reached given that many existing tract identification methods have not been compared. The second point is that a good tract identification method should be highly consistent across different populations and acquisitions (Sydnor et al., 2018; Wasserthal et al., 2018; Yendiki et al., 2011; Zhang et al., 2018c). This is particularly important for automated tract identification methods, which are essential to perform across-lifespan and multi-site studies, which usually involve a large number of datasets (Alexander et al., 2017; Casey et al., 2018; Cetin-Karayumak et al., 2020; Harms et al., 2018; Thompson et al., 2017). One factor that can affect the consistency of methods that segment tractography streamline data is the underlying tractography method that is employed. In general, studies indicate that modern multi-fiber tractography is more sensitive when performing tractography and thus is more consistent across subjects and timepoints than traditional single-fiber DTI tractography (Bucci et al., 2013; Prčkovska et al., 2016). The third point is that anatomical tract identification results can be highly variable across studies due to a lack of consistent fiber tract definitions, where different methods may give different results for the same target anatomical fiber tracts (Dick and Tremblay, 2012; Rheault et al., 2020a; Schilling et al., 2020b). Work is underway to provide sets of consistent rules for fiber tract definitions (e.g. the White Matter Query Language (Wassermann et al., 2016) and tractography-based fiber tract atlases (Mori et al., 2008; Yeh et al., 2018; Zhang et al., 2018c) that are provided in an open fashion for use and possible extension or modification by the community. The fourth point is that a method for performing tractography must be chosen: tract-specific tractography may be more computationally efficient if the number of tracts of interest is small, while whole-brain tractography can be computationally expensive but enables tract identification or parcellation of the whole white matter. (Note that a whole-brain tractogram is required for filtering (Sections 3.3 and 5.3) and analyses of the brain as a network using a connectivity matrix (Sections 5.5 and 5.6)). However, computation of whole-brain tractography considers the entire white matter simultaneously, estimating all fiber tracts using the same set of tractography parameters; this may not be ideal for fiber tracts that are difficult to compute using tractography, e.g., those requiring a lower anisotropy threshold, more lenient curvature threshold, or a dedicated tracking algorithm (such as the optic radiation (Sherbondy et al., 2008; Tax et al., 2014)). Recent approaches propose to better reconstruct white matter anatomy by exploring the tractography parameter space, e.g., by combining results from multiple tractography algorithms (“ensemble tractography”) (Takemura et al., 2016) and by exploring millions of parameter combinations (“augmented fiber tracking”) (Yeh, 2020). The fifth point is that selection of different tract identification methods may require different image registration methods. The ROI-based methods usually require volumetric

registration (e.g., between a population T1-weighted template and individual dMRI data) to align ROIs to the dMRI space. While there are many sophisticated tools to compute these registrations such as FSL (Jenkinson et al., 2012) and ANTs (Avants et al., 2009), the performance is limited by nontrivial factors. For example, the intermodality registration between dMRI and T1-weighted images can be affected by differences in image resolutions (Malinsky et al., 2013) and echo-planar imaging (EPI) distortion in dMRI data (Albi et al., 2018). Many streamline labeling methods use streamline-based registration to directly align individual tractography data to a tractography atlas where a reference tract segmentation is available. Most widely used approaches perform a linear registration (Garyfallidis et al., 2015; O'Donnell et al., 2012), while many studies have proposed to perform non-linear approaches to enable deformations of the streamlines (Benou et al., 2019; Chandio and Garyfallidis, 2020; Olivetti et al., 2016). While using streamline-based registration can avoid the intermodality registration issue in ROI-based methods, streamline registration (especially a nonlinear registration) may be computationally heavier than volumetric registration. Most of the direct segmentation approaches use a training tract segmentation dataset and thus may not require image registration or require a small amount of work for registration (e.g., a rigid volumetric registration); however, we note that curation of a training tract segmentation dataset may require extensive work compared to performing image registration. Lastly, deep learning techniques have been increasingly applied for anatomical tract identification, showing high potential for future work and improvements in computational speed (Chen et al., 2021; Gupta et al., 2017a; 2018; 2017b; Lam et al., 2018; Reisert et al., 2018; Wasserthal et al., 2018; 2019; Xu et al., 2019; Zhang et al., 2020a).

4.2. Parcellation of the whole-brain tractogram

Parcellation of the entire white matter (as represented by a whole-brain tractogram) aims to enable quantitative analysis of all possible white matter connections in the whole brain. There are generally two categories of methods: *cortical-parcellation-based* methods and *fiber clustering* methods (O'Donnell et al., 2013). The cortical-parcellation-based methods are more widely used as they enable construction of a connectivity matrix and its subsequent analysis using techniques from graph theory (as described in Section 5.6) (Bassett and Bullmore, 2017; Bullmore and Sporns, 2009a; Gong et al., 2009a; Ingalhalikar et al., 2014; Sporns et al., 2005; Yeh et al., 2016b; Zalesky et al., 2012). Though relatively less used, fiber clustering tractography parcellation methods are increasingly applied to study the brain's structural connectivity in applications such as disease classification and between-population statistical analysis (Feng et al., 2020; Ji et al., 2019; Wu et al., 2018; Zhang et al., 2018a; 2018b). (Note that these methods could perhaps more correctly be called "streamline clustering," but the term "fiber clustering" is very established in the literature.)

The *cortical-parcellation-based* methods work from a gray-matter-centric perspective. They parcellate tractography according to a cortical (and sometimes a subcortical) gray matter parcellation, focusing on the structural connectivity among different gray matter ROIs (Bassett and Bullmore, 2017; Bullmore and Sporns, 2009a; Gong et al., 2009a; Ingalhalikar et al., 2014; Sporns et al., 2005; Yeh et al., 2016b; Zalesky et al., 2012). Specifically, tractography segmentation is performed by extracting streamlines that connect pairs of ROIs. Therefore the resulting tractography segmentation is mainly determined by the selection

of a cortical parcellation scheme. The majority of methods adopt a cortical parcellation that is computed from T1-weighted or T2-weighted MRI. The most popularly used cortical parcellation is the Freesurfer Desikan-Killiany cortical parcellation (Desikan et al., 2006; Fischl, 2012), while many other cortical parcellation schemes have also been widely used (Destrieux et al., 2010; Shattuck et al., 2008; Tzourio-Mazoyer et al., 2002). Many cortical-parcellation-based methods have also used a functional cortical parcellation computed using functional MRI data (Eickhoff et al., 2005; Glasser et al., 2016; Schaefer et al., 2018; Yeo et al., 2011). Finally, an alternative approach is to use a vertex-wise cortical "parcellation," i.e., by identifying streamlines that connect pairs of vertices in the cortical surface (Besson et al., 2014; Fellner et al., 2020; Tian et al., 2021). Currently, there is no consensus about which brain parcellation technique could be most useful (de Reus and Van den Heuvel, 2013; Yeh et al., 2020; Zalesky et al., 2012).

The *fiber clustering* methods work instead from a white-matter-centric perspective. They group tractography streamlines according to their geometric trajectories, describing the structural connectivity according to the white matter anatomy (Avila et al., 2019; Chekir et al., 2014; Garyfallidis et al., 2018; Guevara et al., 2012; Li et al., 2010; O'Donnell and Westin, 2007; Román et al., 2017; Ros et al., 2013; Siless et al., 2018; 2020; Tunç et al., 2014; Vázquez et al., 2020; Wu et al., 2020a; Yeh et al., 2018; Yoo et al., 2015; Zhang et al., 2018c; Ziyan et al., 2009). In general, fiber clustering methods start with a computation of pairwise streamline geometric similarities, followed by a computational clustering method to group similar streamlines into clusters. Compared to the cortical-parcellation-based methods that focus on streamline terminal regions, fiber clustering methods leverage the full lengths of the streamline trajectories. As a result, the cortical-parcellation-based methods can erroneously group streamlines that follow completely different trajectories through the white matter but nevertheless end up at the same gray matter endpoints, whereas fiber clustering can be insensitive to streamlines diverging at the cortex if they pass through the same deep white matter regions. In addition, unlike the cortical-parcellation-based methods that leverage additional cortical parcellation information, the majority of fiber clustering methods work on tractography data *only*, such that there is no need for an inter-MR-modality registration, e.g., an image registration between dMRI and T1w images that can be affected by differences in image resolution (Malinsky et al., 2013) and echo-planar imaging (EPI) distortion in dMRI data (Albi et al., 2018). Due to these factors, several studies have demonstrated advantages of fiber clustering methods over the cortical-parcellation-based methods, including more consistent parcellation across subjects (Sydnor et al., 2018; Zhang et al., 2017) and a higher reproducibility between test-retest scans (Zhang et al., 2019).

When choosing a method to perform parcellation of the entire white matter, the previously described points related to reproducibility and consistency of anatomical tract identification across different populations and acquisitions (as described in Section 4.1) are also important facts to consider (Buchanan et al., 2014; Smith et al., 2015a; Zhang et al., 2019; 2018d).

An additional point to be highlighted for parcellation of the entire white matter is the scale or the granularity of the parcellation, i.e., how many white matter parcels are to be obtained after parcellation. For constructing the connectome, this is related to the choice of the cortical parcellation (Hagmann et al., 2008a; Messé, 2020), while for fiber

clustering this is related to the number of fiber clusters obtained by the clustering algorithms (Wu et al., 2020a; Zhang et al., 2018c). Various parcellation scales have been applied in different studies, ranging from tens to millions of white matter parcels (Besson et al., 2014; Liu et al., 2017; Osmanlıoğlu et al., 2020; Rodrigues et al., 2013; Zalesky et al., 2010; Zhang et al., 2018a). Choosing parcellation scales depends on the target application, e.g., studies have suggested a fine scale white matter parcellation (over 2000 parcels) can be beneficial for machine learning and statistical analysis (Liu et al., 2017; Zhang et al., 2018a) while a coarse scale parcellation (fewer than 200 parcels) can improve the connectome consistency across individuals (Osmanlıoğlu et al., 2020; Rodrigues et al., 2013). We note that inter-subject connectome consistency may also be improved using other approaches, e.g., consistency-based thresholding (Baum et al., 2018; Roberts et al., 2017).

5. Performing quantitative analysis: methods for tractography quantification

The goal of tractography quantification is to extract quantitative measures that are useful to assess the structural connectivity of the brain's white matter pathways. In this section, we will first introduce the quantitative measures that can be computed from tractography (Section 5.1). Then we will focus on how to extract these measures within an individual white matter fiber pathway (Section 5.2) and how to perform filtering techniques to reduce potential biases in the extracted measures (Section 5.3). Next, we introduce how the extracted measures can be used for tract-specific analysis of anatomical white matter tracts (Section 5.4) and for computing the edge weights to construct a connectivity matrix (Section 5.5). Finally, we will introduce topological analyses of whole-brain connectivity based on graph theoretical measures and more advanced connectome measurements (Section 5.6).

5.1. Quantitative measures computed from tractography

There are many quantitative measures that can be computed from tractography, which can be subdivided into two categories based on the source of data used to compute the measures. The first category of quantitative measures are based on *the tractography data alone*, which are often used to define the connectivity strength (Jones, 2010; Smith et al., 2020a; Sotiropoulos and Zalesky, 2019; Yeh et al., 2020). The number of streamlines (NOS) is one widely used measure to quantify the connectivity strength (Hagmann et al., 2008b; Ingalhalikar et al., 2014; Roberts et al., 2016; Sporns et al., 2005; van Dellen et al., 2018). Several studies conducted on animals using invasive tract-tracing techniques have shown good agreement between the NOS and the biological connectivity as measured using *ex vivo* tract-tracing data (Delettre et al., 2019; Girard et al., 2020; van den Heuvel et al., 2015a). However, because of the difference in resolution between the measured dMRI signal and actual axon dimensions (as described in Section 3.3: "Connection density biases"), many studies have emphasized that NOS does not provide a truly quantitative measure of connection strength (Jones, 2010; Jones et al., 2013; Sotiropoulos and Zalesky, 2019; Yeh et al., 2020). Recent work aims to provide alternative, more quantitative measures of connectivity that better estimate the underlying connection density (Smith et al., 2020a) or modulate streamline contributions toward aggregate measures of connectivity (see Section 5.3). Other quantitative measures can be computed directly from tractography, such as the

volume and the length of a fiber tract (Bajada et al., 2019; Behrman-Lay et al., 2015; Catani et al., 2007; Chandio et al., 2020a; Colby et al., 2012a; Grinberg et al., 2018; Rheault et al., 2020a; Song et al., 2015; Yeatman et al., 2012), have also been used.

The second category of quantitative measures computed from tractography leverages microstructural measures that are usually computed from a diffusion model (e.g., diffusion tensor model) or another quantitative imaging modality (e.g., myelin imaging). In this category of measures, tractography is generally used to define the locations in which microstructural measures are sampled. (This sampling may be done after performing tractography, or during performing tractography as part of sampling or computing a diffusion model). The most widely used microstructural measures are based on computational modeling of the dMRI signal. Popularly used diffusion-modeling-based microstructural measures include the fractional anisotropy, axial, radial and mean diffusivities (FA, AD, RD and MD respectively) derived from traditional diffusion tensor model (Basser and Pierpaoli, 1996). More advanced measures include those reflecting inter- and intra-cellular signal fractions derived from Diffusion Kurtosis Imaging (DKI) (Jensen and Helpern, 2010), Free Water modeling (Pasternak et al., 2012; 2009), Neurite Orientation Dispersion and Density Imaging (NODDI) (Zhang et al., 2012), Spherical Mean Technique (SMT) (Kaden et al., 2016), or Apparent Fiber Density (AFD) (Raffelt et al., 2012). It is important to be aware that changes in dMRI microstructural measures can be non-specific, in part due to the difference in scales between voxel-averaged dMRI signals (mm scale) and the scale of the individual axons and cells that are probed by the diffusing water (micrometer scale). For example, many factors (e.g., cell death, edema, gliosis, inflammation, change in myelination, increase in connectivity of crossing fibers, increase in extracellular or intracellular water, etc.) may cause changes in FA (Assaf and Pasternak, 2008; Jones et al., 2013; Le Bihan and Johansen-Berg, 2012). More details about sensitivity, specificity and interpretability of these microstructural measures are out of the scope of the present review but the reader can refer to the following studies (Alexander et al., 2019; Jelescu and Budde, 2017; Novikov et al., 2019; 2018). Other approaches for tractography quantification leverage information from imaging modalities other than dMRI, such as T1-weighted (T1w) imaging (Boshkovski et al., 2020a; Yeatman et al., 2014a), myelin sensitive maps (Lee et al., 2020; Mancini et al., 2020; Piredda et al., 2021) and g-ratio (Campbell et al., 2018). For example, researchers have used the longitudinal relaxation rate (R1), a measure sensitive to myelin, along the fiber tracts (Boshkovski et al., 2020a; Yeatman et al., 2012).

These microstructural measures can be computed along fiber pathways using several approaches. Usually, this is done by computing a model in each voxel to derive a 3D microstructural map (e.g., an FA image) and then using tractography to define the locations from which the values of this microstructural measure should be sampled. This sampling may be done by first generating a binary mask that defines the voxels through which streamlines pass and then sampling from an underlying microstructure image within this mask (Ciccarelli et al., 2003; Heiervang et al., 2006; Kunimatsu et al., 2004; Voineskos et al., 2010). The sampling may alternatively be done by sampling microstructural measures at each point of the streamlines from a pre-calculated microstructure image (Ciccarelli et al., 2003; Heiervang et al., 2006; Kunimatsu et al., 2004; Voineskos et al., 2010). Instead of using a pre-calculated microstructure image, the diffusion or fiber model can

be simultaneously estimated when performing tractography so that the microstructural measures are directly computed at points along each streamline (Girard et al., 2017; Gong et al., 2018; Malcolm et al., 2010; Olszewski et al., 2017; Reddy and Rathi, 2016).

5.2. Domain of analysis: extraction of quantitative measures within white matter fiber pathways

After choosing a quantitative measure of interest (Section 5.1) and a method for tractography segmentation (Section 4), then there are many methods available to extract the measure within an individual white matter fiber pathway. This is important to enable tract-specific analysis (Section 5.4) and construction of a connectivity matrix (Section 5.5). Two main strategies can be employed: using a scalar value as a summary statistic, or using data along the length of the fiber pathway.

The most commonly adopted strategy for extraction of quantitative measures is to compute a *scalar value* as a summary statistic of the fiber pathway. (This is required for connectome-based analysis and is a popular approach for tract-specific analysis). While some quantitative measures intrinsically provide a single scalar value per pathway, e.g. NOS or tract volume, others (e.g. sampled values of a quantitative metric) necessitate calculation of some statistic in order to produce such a scalar. For microstructural measures, the *mean measure within the fiber pathway* is the most widely used. Other summary statistics such as the *median, maximum* and *minimum* have also been employed (Boshkovski et al., 2020b; Zhang et al., 2018a; 2018b). A summary statistic can be obtained in several ways according to how microstructural measures are computed along fiber pathways (as described in Section 5.1). It can be computed within a binary mask defining a fiber pathway in a microstructure image (e.g. the mean FA within the mask) (Ciccarelli et al., 2003; Heiervang et al., 2006; Jolly et al., 2021; Kunimatsu et al., 2004; Voineskos et al., 2010; Wilson et al., 2021). It can also be computed by averaging microstructural measures sampled along each point of the streamlines (Gong et al., 2018; Jones et al., 2006; Olszewski et al., 2017; Zhang et al., 2018a; 2019). The choice of the best summary statistic for data measured within a fiber pathway is still open. For example, compared to the mean statistic, studies have shown that the median can be more robust against outliers and does not rely on the normality assumption for the distribution of the microstructure parameter along a streamline (Boshkovski et al., 2020b; Zhang et al., 2018b). One study has suggested that the maxima and minima are more discriminative than the mean value in machine-learning-based disease classification (Zhang et al., 2018a).

The second strategy to quantify an individual fiber pathway is to measure the distribution of the microstructural measures *along* the fiber pathway. This can enable the study of the tissue microstructure in local regions along the fiber pathway. This approach requires definition of a coordinate system, sampling framework, or surface-based representation to define how to sample the microstructural data of interest (Bells et al., 2011a; Chen et al., 2016b; Colby et al., 2012b; Corouge et al., 2006; Goodlett et al., 2009; Irimia et al., 2020; Jones et al., 2005; O'Donnell et al., 2009; Yeatman et al., 2012; Yeh, 2020). Most often, data are averaged across corresponding points along each streamline in the pathway, such that data can be analyzed (e.g., an along-tract or along-pathway plot) versus streamline arc length or other

parameterization (Colby et al., 2012b; Corouge et al., 2006; Yeatman et al., 2012). Other approaches fit a medial surface representation to the pathway, such that sampled data can be represented in two dimensions and can be analyzed not only along the pathway but also across its cross-section (Chen et al., 2016b; Qiu et al., 2010; Yushkevich et al., 2009).

5.3. Quantitative measures using filtering techniques

The so called filtering methods discussed in Section 3.3 can also be used to perform "microstructure-informed" tractography with the aim to extract quantitative measures of white matter fiber pathways and reduce potential bias in the estimation of connectivity. Assuming that the microstructure properties corresponding to a single streamline remain constant along its path, these methods assign a specific microstructural property to each reconstructed pathway. The underling assumption comes from the fact that a streamline reconstructed from tractography cannot represent a single axon, but rather a group of axons following the same trajectory, and thus we can suppose that on average the microstructure properties the magnetic resonance signal is sensitive to at achievable resolution remain constant. While in its original implementation SIFT (Smith et al., 2013) provides only the NOS adjusted based on voxel-wise spherical deconvolution, its evolution SIFT2 (Smith et al., 2015b) optimizes per-streamline cross-section multipliers to match a whole-brain tractogram to fixel-wise fiber densities and thus provides a value for each streamline that can be used (for example) to define the edge weights of the connectome. Similarly, LiFE (Pestilli et al., 2014), COMMIT (Daducci et al., 2013; 2014; Schomburg and Hohage, 2019), COMMIT2 (Schiavi et al., 2020a) and COMMIT2$_{tree}$ (Ocampo-Pineda et al., 2021) deconvolve the measured dMRI signal on the streamlines and assign a single contribution, or "weight", to each one of them using classical multi-compartment models (Panagiotaki et al., 2012). These methods have been used to investigate properties of healthy and pathological brains, showing better performance than the standard NOS (Schiavi et al., 2020b; Smith et al., 2015a; Yeatman et al., 2014b). In particular, because of their flexible implementations, COMMIT, COMMIT2 and COMMIT2$_{tree}$ allow complementing tractography with biophysical models of the tissue microstructure and, thus, enable one to access more quantitative and biologically informative features of individual bundles, such as average axon diameter (Barakovic et al., 2018), myelin content (Schiavi et al., 2019) and bundle-specific T2 (Barakovic et al., 2021b).

5.4. Tract-specific analysis using statistical or machine learning techniques

Once a quantitative measure has been extracted for individual fiber pathways, several options exist for tract-specific analysis, which may be hypothesis-driven using statistical analysis or data-driven using machine learning. These methods may rely on a summary statistic per tract, or analyze data along a tract.

One widely used analysis is based on a hypothesis-driven strategy to assess if there are statistical differences of tract(s)-of-interest between groups (e.g., between health and disease, or between different subtypes of a disease). Usually, given a quantitative measure of interest, a selected summary statistic (e.g. mean of the chosen microstructural measure) is extracted from the tract(s)-of-interest and is used to compute the level of group differences (e.g., the p-value) using statistical group-wise comparison methods such as Student's t-test,

ANOVA, or other more advanced statistical analysis methods (Habeck and Stern, 2010; Martí-Juan et al., 2020; Ombao et al., 2016; Zhang et al., 2018b). Another hypothesis-driven analysis uses a regression model (e.g., a generalized linear model (Dobson and Barnett, 2018) or support vector regression (Zhang and O'Donnell, 2020)) to assess correlation of the tract quantitative measurement and a behavioral or a disease symptom score. Such analyses have been applied to study, e.g., how white matter fiber tracts are affected in individuals with different disease severity (Cha et al., 2015; Chiang et al., 2016; Price et al., 2007), how tracts relate to cognitive and socio-emotional function (Zekelman et al., 2021), and how tracts are developing during human neurodevelopment and aging (Gertheiss et al., 2013; Hasan et al., 2009a; Michielse et al., 2010). One important point to note is that correction for multiple comparisons is needed if there are multiple tracts and/or multiple quantitative measurements analyzed. Commonly used multiple comparison correction methods include false discovery rate (FDR) (Benjamini and Hochberg, 1995) and Bonferroni (Holm, 1979) methods. However, it is important to highlight that such multiple comparison correction methods, which assume independence across data samples, can be overly conservative when applied to tests performed on multiple tracts and/or quantitative measurements that are not independent. For example, MD and FA are not mutually mathematically orthogonal measures (Ennis and Kindlmann, 2006).

Another tract-specific analysis strategy is data-driven and uses machine learning techniques to perform tasks such as disease classification and prediction (Deng et al., 2019; O'Dwyer et al., 2012; Payabvash et al., 2019; Zhang et al., 2018a), as well as prediction of behavioral measures and traits (Seguin et al., 2020a; Tian et al., 2021). In machine learning analysis, the quantitative measures computed from individual fiber pathways are treated as feature descriptors, which are input to a machine learning algorithm (e.g., a support vector machine) to train a model from a set of training samples with known information (e.g., labels such as disease or healthy control). Then the trained model can be used to predict new samples. Unlike statistical analysis methods that usually aim to find white matter structures with statistical group differences, the machine-learning-based methods aim to offer predictive relevance. This can be advantageous in situations where the within-group heterogeneity is large (e.g., in psychiatric diseases) and thus a statistical group comparison, which essentially compares the "average patient" to the "average control," is not informative. Another advantage of machine learning is that it can be easily applied to multimodal data. For example, the combination of structural and functional connectivity measures has been shown to increase predictive power (Whitfield-Gabrieli et al., 2016).

Instead of using a single scalar value to summarize the entire pathway, many methods perform along-tract analysis to investigate the distribution of the microstructural measures along the fiber pathway (variously called "tractometry," "profilometry," and "tract-based morphometry") (Bells et al., 2011b; O'Donnell et al., 2009; Yeatman et al., 2012). Along-tract analysis enables the study of local regions along the tract. After mapping microstructural measures along each point of the streamlines along the fiber pathway, a widely used strategy is to analyze data along the tract profile. One popular approach is to average data across corresponding points along each streamline in the pathway and leverage a prototype, core, or mean streamline to enable statistical analysis comparing subjects or groups (Colby et al., 2012b; Wang et al., 2016; Yeatman et al., 2012). Other

approaches can employ streamlines of the entire tract in the statistical analyses (Chandio et al., 2020b). Additional studies have analyzed tracts represented as surfaces (Chen et al., 2016b; Qiu et al., 2010; Yushkevich et al., 2009) or performed data reduction techniques to reduce the dimensionality of the point-wise measurements along tracts (Ceschin et al., 2015; Chamberland et al., 2019; Geeraert et al., 2020). Several studies have shown that along-tract analysis can be more sensitive to detect differences that are not apparent in the mean value within the tract (Colby et al., 2012b; O'Donnell et al., 2009; St-Jean et al., 2019).

5.5. Construction of a structural connectivity matrix

Quantitative measures extracted for individual fiber pathways can also be used to construct a structural connectivity matrix to map the whole-brain network of structural connectivity between all pairs of gray matter regions (Hagmann et al., 2008a; Sporns et al., 2005). This approach is motivated by a general shift of focus away from the roles of isolated regions towards understanding the brain as a networked system (Barch et al., 2016; Friston, 2002). Construction of the connectivity matrix has been described in several reviews (Sotiropoulos et al., 2016; Yeh et al., 2020) and includes two major steps. First, parcellation of the whole-brain tractogram is needed to compute all possible fiber pathways in the brain, i.e., white matter parcels connecting all pairs of gray matter regions (as described in Section 4.2). Then, a metric of "connectivity" is needed to define quantitative edge weights in the connectivity matrix (see Fig. 1(e) for a graphic illustration). This is usually done by computing a scalar value for each white matter parcel (as described in Section 5.2). The most popular scalar value for connectivity matrix analysis is the NOS (Hagmann et al., 2008b; Ingalhalikar et al., 2014; Roberts et al., 2016; Sporns et al., 2005; van Dellen et al., 2018), where higher values are considered to indicate stronger connectivity between pairs of gray matter regions. Other scalar values that are generally interpreted as measures of connectivity "strength" include microstructural measures, e.g., FA (Bathelt et al., 2017) and R1 (Boshkovski et al., 2020a). For scalar values that are interpreted as inversely related to connectivity "strength," such as RD, MD, or maps reflecting extracellular or isotropic/free water components of the signal, a transformation of the connectivity matrix may be performed using the reciprocal or the log function prior to any subsequent connectivity analysis (Fornito et al., 2016).

While the construction of the connectivity matrix is straightforward, multiple factors that need careful consideration have been pointed out by researchers. Selection of a gray matter parcellation scheme (as described in Section 4.2) is the first essential consideration when constructing a structural connectivity matrix, and it has been shown to be highly consequential in connectome analysis (de Reus and Van den Heuvel, 2013; Yeh et al., 2020; Zalesky et al., 2012). Myriad components of the processing pipeline can also influence the resulting connectome matrix data, even down to the level of detail of the mechanism by which streamlines are assigned to those parcels (Yeh et al., 2019a). In addition, connectomes are usually post-processed to reduce potential bias in the estimation of graph measures. This step is typically done by simply thresholding according to some rule or to reach a predefined density, or using filtering techniques described in Section 5.3. Selection of tractography filtering strategies is important and has been shown to affect the analysis of the topology of brain networks (Civier et al., 2019; Frigo et al., 2020; Yeh et al., 2016a) and

affect sensitivity and specificity when analyzing the connectomes (Zalesky et al., 2016a). Moreover, as concluded in several studies (Bastiani et al., 2012; Qi et al., 2015; Yeh et al., 2016a), several other factors (such as q-space sampling schemes, fiber orientation models, and tractography algorithms) that are not specifically reviewed in our paper, have also been shown to affect most network measures derived from the connectivity matrix.

5.6. Graph theoretical measures and advanced structural connectome measurements

A structural connectivity matrix defines a network (or *graph*) of whole-brain anatomical connectivity, where the nodes are typically gray matter regions or ROIs, and the edges represent the connectivity between these regions (Hagmann et al., 2008a; Sporns et al., 2005) (Fig. 4a). The disciplines of graph theory and network science provide a framework to quantify network properties of brain connectivity (Rubinov and Sporns, 2010) and investigate whole-brain models of structural wiring (Betzel et al., 2016). Over the last two decades, the study of the brain as a network has become increasingly popular in the neuroscience and neuroimaging communities, giving rise to the new fields of connectomics and network neuroscience (Bassett and Sporns, 2017; Fornito et al., 2013; 2015; 2016).

A daunting number of graph theoretical measures have been proposed to study the network properties of the brain's connectome (Bullmore and Sporns, 2009b; Iturria-Medina et al., 2008; Rubinov and Sporns, 2010). The choice of which measures to focus on is dependent on the research questions and hypotheses at hand. Graph measures can be classified based on their resolution or scope—from local measures that quantify properties of individual ROIs (nodes), to mesoscale measures describing clusters of interconnected ROIs, to global measures that describe whole-brain connectivity properties (Betzel and Bassett, 2017; Fornito et al., 2016) such as network communication in the brain (Graham et al., 2020) (Fig. 4b). In the following paragraphs, we give examples of these popular graph measures that quantify aspects of brain networks at each level, from local to global.

At the local level, node centrality measures provide a useful characterization of the integrative importance of individual brain regions (Sporns et al., 2007). Degree and strength are the simplest and most popular node centralities, quantifying, respectively, the number of connections and the sum of connection weights of individual regions (see Oldham et al., 2019 for a review on advanced node centrality measures). Centrality measures find particular utility in identifying hub regions that may play a central role in integrative brain function (van den Heuvel and Sporns, 2013). Indeed, hubs identified with these measures have been found to entail high metabolic expenditures and be disproportionately implicated in brain disorders (Crossley et al., 2014; Fornito et al., 2015).

At the mesocale, structural connectivity can be partitioned into modules (also known as communities) that reflect the presence of clusters embedded in the brain's wiring (Betzel, 2020; Sporns and Betzel, 2016). The practice of uncovering such clusters, called community detection or modular decomposition, helps to summarize the complexity of structural networks into coarse-grained blocks, aiding the identification of meaningful sub-networks and connectivity motifs relevant to specific research questions. Typically, ROIs belonging to the same module are densely and strongly interconnected, while connectivity between modules is sparse. This modular structure constrains the flow of information through the

network in a manner thought to promote functional segregation and clusters of specialized information processing (Betzel et al., 2013). Popular methods for community detection in structural brain networks include the Louvain algorithm and stochastic block models, though determining best practices around the utilization of these and other approaches remain an active topic of research (Fortunato and Hric, 2016).

At a global scale, graph measures can be used to describe how the brain's structural wiring supports the communication of information between distant ROIs and cognitive systems (Avena-Koenigsberger et al., 2018; Mišić et al., 2015). While structurally connected regions can directly communicate, signal propagation between unconnected ROIs requires a sequence of one or more intermediate connections to enable communication. Graph measures of network communication presume that the strength of structural connections reflects the capacity of fiber bundles to support fast and reliable propagation of electrical signals. Connections with, e.g., large NOS, high integrated FA, or short average streamline length are typically considered to support efficient network communication. Traditionally, connectome communication has been quantified using graph measures based on the notion that neural information transfer occurs via topological shortest paths. Shortest-path-based measures include, e.g., the popular characteristic path length and network efficiency (Rubinov and Sporns, 2010). However, algorithmically, the identification of shortest paths demands individual regions to possess global knowledge of structural connectivity, a requirement unlikely to be met in decentralized systems such as the brain (Avena-Koenigsberger et al., 2019; Goñi et al., 2014; Seguin et al., 2018). In addition, connectome networks are known to strike a balance between wiring minimization (shortest paths) and formation of connections between brain regions with similar connectivity profiles (homophily) (Betzel et al., 2016).

In light of these shortcomings, recent work has stated to focus on alternative models of connectome communication, such as network diffusion (Estrada and Hatano, 2008; Goñi et al., 2014), linear transmission models (Mišić et al., 2015), and navigation (Seguin et al., 2018) (see Avena-Koenigsberger et al., 2018 for a review). Determining which approaches most accurately reflect underlying biological processes remains a crucial open question (Seguin et al., 2020b). Nonetheless, recent work has shown that advanced communication measures can elucidate how the organization of structural connectivity shapes the brains functional dynamics (Goñi et al., 2014; Imms et al., 2021; Mišic et al., 2018; Wang et al., 2019). For instance, despite the inherent limitations of dMRI tractography in resolving axonal fiber directionality, graph measures computed on the undirected human connectome can reveal patterns of asymmetric communication, as evidenced by significant associations to the directionality of effective connectivity computed using dynamic causal modeling (Seguin et al., 2019). Therefore, the use of advanced communication measures enables the study of directional and asymmetric functional interactions from structural connectivity mapped with dMRI.

6. Applications of quantitative tractography analysis

In the last two decades, modern dMRI-based tractography that offers quantitative measurements of fiber tracts has extended neuroanatomy methods and become a key

technique for the study of the brain's white matter in a wide range of applications. In this section, we focus on several essential areas including development, aging, neurological disorders, mental disorders, and neurosurgery. These studies can be organized into two types that correspond to the above-mentioned tract-specific and connectome-based analyses. The first category concerns major fiber pathways or localized structural connectivity in order to capture fine-grained details of brain circuits. The second category regards the entire white matter as a complex system and thus adopts clustering analysis for feature reduction or utilizes graph theoretical analysis to quantify topological characteristics with respect to information integration and segregation.

6.1. Developmental tractography of the brain

Brain white matter undergoes highly ordered changes during the ontogeny from a neural tube to a complex connectome. In the past decade, researchers have implemented dMRI tractography investigations across broad brain developmental stages ranging from the middle fetal stage to adulthood (Cao et al., 2017; Dubois et al., 2014; Gilmore et al., 2018; Huang, 2010; Lebel and Deoni, 2018; Lebel et al., 2019; Qiu et al., 2015; Zhao et al., 2019b).

For the prenatal stage, most tractography studies aim to identify the migration pathways of neurons and emergence of key tracts of the brain as important developmental milestones (Dubois et al., 2014; Gilmore et al., 2018; Huang, 2010; Vasung et al., 2019). For instance, using *ex vivo* dMRI scans on fetal brain samples, researchers are able to identify the major tract parts of the fornix and cingulum bundles at 13 weeks, but a part of the corpus callosum at 15 weeks (Huang et al., 2009). Similar studies also show that the radial and tangential pathways organization are prominent at 17 weeks but gradually disappear at later gestational ages, and all major structural pathways are already identifiable by term (Takahashi et al., 2002). These results are consistent with classical histological studies (Mitter et al., 2015; Vasung et al., 2010). Due to recent advances in methodological progress such as motion correction algorithms, *in vivo* tractography on the fetal brain has become available and exhibit highly agreement with *ex vivo* and neuroanatomical studies (Christiaens et al., 2021; Khan et al., 2019), which indicates strong potential for future prenatal brain investigations.

In the postnatal stage, *in vivo* tractography offers a superior tool to chart the spatiotemporal maturation patterns of the reconstructed tracts by employing quantitative dMRI metrics from the infancy period (Dubois et al., 2014; Gilmore et al., 2018; Lebel and Deoni, 2018; Qiu et al., 2015; Vasung et al., 2019) to the adolescent stage (Lebel et al., 2019; Tamnes et al., 2018). Despite focusing on different developmental ranges, these studies consistently observe significant age-related increases of FA and MD in widespread fiber tracts during postnatal growth in both cross-sectional and longitudinal population designs (Lebel and Deoni, 2018). Studies also characterize several typical nonlinear trajectories (piecewise, exponential and quadratic) of diffusion metrics for major tracts across large developmental ranges such as infancy to childhood (Pecheva et al., 2017; Reynolds et al., 2019; Stephens et al., 2020) or adolescence to adulthood (Chang et al., 2015; Lebel and Beaulieu, 2011). Researchers can further estimate the growth of tracts at the subsystem level by multivariate analysis; for example, one study investigated the maturational calendars of linguistic bundles

and found that the dorsal pathway development falls behind the ventral pathway at birth and catches up later at the first postnatal months (Dubois et al., 2016).

Using the newly emerging developmental connectomics framework, researchers are able to seek the wiring principles of brain white matter tracts (Cao et al., 2017; 2016; Collin and Van Den Heuvel, 2013; Gilmore et al., 2018; Ouyang et al., 2019; Tymofiyeva et al., 2014; Vértes and Bullmore, 2015; Zhao et al., 2019b). Many studies have discovered largely adult-like topological structures including significant small-world, modular, and rich-club organization during the middle to final trimester of gestation (Brown et al., 2014; Song et al., 2017; Tymofiyeva et al., 2013; Van Den Heuvel et al., 2015b; Zhao et al., 2019b), which reveals that the whole brain tract network is already highly efficient and specialized around term age. During prenatal development, the whole network becomes increasingly efficient and segregated with typical system-level refinements such as increased small-worldness (Brown et al., 2014) and increased modularity (Van Den Heuvel et al., 2015b). After birth until adulthood, the brain network reshapes to improve integration capacity with the reconfigurations of decreased modularity and decreased small-worldness (Chen et al., 2013; Dennis et al., 2013; Hagmann et al., 2010; Huang et al., 2015; Tymofiyeva et al., 2013). In terms of regional changes, although neonatal brains already show similar structural hub distribution as adult brains, many refinements occur for the topological roles for each node (Yap et al., 2011). The nodal efficiency of provincial hubs and the strength of within-module connections (Zhao et al., 2019a) develop fast during the prenatal stage, and hubs expand into the inferior frontal and insula regions at term age (Ball et al., 2013; Van Den Heuvel et al., 2015b). After birth, the left anterior cingulate gyrus and left superior occipital gyrus become hubs in toddler brains (Huang et al., 2015). The centrality of the pre-cuneus and cuneus still increases before pre-adolescence (Huang et al., 2015; Yap et al., 2011).

The interpretation of the above tract-related changes largely depends on the corresponding biological changes during development. In the fetal brain, it is probably caused by pre-myelination phases such as proliferation and maturation of oligodendrocyte and progenitor cells, the glia that form the myelin sheath (Jakovcevski et al., 2009). In the early postnatal stage, ongoing myelination is a clear cause (Paydar et al., 2014) while axonal packing and decreasing water content (Neil et al., 2002) may also make a contribution. In later childhood and adolescence, results seem to be attributed to changes of neurite density, particularly axonal packing (Lebel and Deoni, 2018).

6.2. Aging and lifespan tractography of the brain

Aging is associated with broad alterations of axon density and axonal structure. Researchers have performed many tractography investigations to trace the normal aging patterns and lifespan trajectories of brain connectivity across wide age ranges, spanning childhood until old age (Collin and Van Den Heuvel, 2013; Madden et al., 2009; Moseley, 2002).

Early tractography studies usually estimated the aging effect on specific fiber bundles such as the corpus callosum (Sullivan et al., 2006), uncinate fasciculus (Hasan et al., 2009a), and fornix (Stadlbauer et al., 2008b), which show consistent changes including decreased FA, increased MD and decreased tract volume. By subdividing across or along certain tracts (as described in Section 5.4), researchers have been able to delineate the elaborate aging

patterns within a tract (Davis et al., 2009; Michielse et al., 2010; Sullivan et al., 2006). For instance, FA values of the corpus callosum declined with aging only in the genu part while not in the body and splenium parts in participants aged 22–84 years (Michielse et al., 2010). Using various tract identification methods, many studies have investigated a wide range of tracts (Davis et al., 2009; Stadlbauer et al., 2008a; Sullivan et al., 2010; Westlye et al., 2010), revealing a typical spatial degeneration pattern across brain systems in which prefrontal association tracts are the most vulnerable to aging, while cingulum, temporal and parietal-occipital commissural connections are relatively preserved. From a lifespan view (Hasan et al., 2010; 2009b; Lebel et al., 2010; 2012; Yeatman et al., 2014a), although most tracts show increased FA during childhood and adolescence and decreased FA at older ages, the age when FA reaches its highest peak varies across different white matter tracts. In general, the anterior and posterior parts of tracts peak earlier than the central part of tracts, around 20 to 40 years old (Lebel et al., 2010), supporting a classical “last-in-first-out” theory. Recently, with increasing numbers of adult imaging datasets and development of automated tract identification pipelines (as described in Section 4.1), researchers have began to assess the effect of aging on the brain’s tracts by employing thousands of participants (Cox et al., 2016; de Groot et al., 2015; Tseng et al., 2021), which brings us into an unprecedented “big data” era (Xia and He, 2017).

From a connectomics perspective (as described in Section 5.6), tractography studies show that the basic layouts of the brain’s structural network are largely preserved until old age, such as the economical small-world character, the modular organization and rich club organization (Gong et al., 2009b; Li et al., 2020c; Wen et al., 2011; Wu et al., 2012a). Meanwhile, both global and local alterations of the brain’s structural topology occur with aging, including decreased network efficiency (Bi et al., 2021; Gong et al., 2009b; Li et al., 2020c; Madden et al., 2020; Shu et al., 2018b; Wu et al., 2012a) and decreased inter-/intra-modularity strength that may be due to the widespread degeneration of whole brain tracts (Li et al., 2020c; Wu et al., 2012a) and loss of frontal hubs that may be driven by the vulnerable prefrontal tracts (Zhao et al., 2015). These tractography-based network changes may offer potential imaging markers for individualized cognition. As strong evidence, a recent large sample study implicates the global dimensions of variation in the human structural connectome in aging-related cognitive decline (Madole et al., 2020). Lifespan changes of the connectome also show good consistency with cognitive maturation (Zhao et al., 2015). For instance, following an inverted U-shaped trajectory, the peak ages of network efficiency and small-world measures (30 years) fall within the range of peak ages on general cognitive performance (Schaie, 2005; Schroeder and Salthouse, 2004), and brain regions within the default mode network, which is involved broadly in high-level cognition (Raichle, 2015; Vatansever et al., 2018; 2017), display the latest maturation age of peak.

These various tract-related changes could be attributable to different physiological brain changes at older ages. For instance, decreased axonal density and loss of fibers may cause a decline of FA values, while an increased amount of water content along with healthy atrophy may cause increased MD (Moseley, 2002). Results from a study that employ an advanced diffusion model (NODDI) indicate that the age-related declines in FA are primarily induced by declines in neurite density rather than changes in tract complexity (Cox et al., 2016). Using multi-modal dMRI and PET imaging analysis, researchers further interpreted the

metabolic mechanisms underlying aging-related changes of brain tractography, in which they found that the overall connectome efficiency-metabolism coupling across brain regions significantly increased with aging (Bi et al., 2021).

6.3. Tractography in neurological and mental brain disorders

dMRI tractography has become an indispensable tool for studies on various brain disorders including, but not limited to, multiple sclerosis (MS) (Fleischer et al., 2019; Sbardella et al., 2013), amnestic mild cognitive impairment (aMCI) (Bai et al., 2009; Zhao et al., 2017a), Alzheimer's disease (Jack and Holtzman, 2013; Lo et al., 2010; Mito et al., 2018; Toga and Thompson, 2013), stroke (Mukherjee, 2005), schizophrenia (Collin et al., 2016; Goldsmith et al., 2018; Wheeler and Voineskos, 2014), depression (De Witte and Mueller, 2017; Korgaonkar et al., 2014), obsessive-compulsive disorder (OCD) (Cao et al., 2021; Chiu et al., 2011; Gan et al., 2017; Gruner et al., 2012; Koch et al., 2014; Widge et al., 2021), attention-deficit hyperactivity disorder (ADHD) (Cao et al., 2014; 2013; Damatac et al., 2020; Hong et al., 2014) and autism (Ikuta et al., 2014; Langen et al., 2012; Thomas et al., 2011; Zhang et al., 2018a). In this section, we are condensing the explanation using two exemplar disorders, *multiple sclerosis* and *schizophrenia*, as the methods utilized in the study of such are representative of the work done across a breadth of disorders. Compared to traditional voxel-based analysis, quantitative tractography not only offers an irreplaceable tool to accurately quantify the abnormalities along local trajectories of fiber bundles *in vivo* but also provides a unique opportunity to investigate brain diseases at a network level (Collin et al., 2016; Fleischer et al., 2019; Wheeler and Voineskos, 2014).

6.3.1. Multiple sclerosis—Multiple sclerosis is a demyelinating disease with multiple focal white matter lesions (Fleischer et al., 2019). Accurate quantification of tract-specific damage is especially important for patients in MS because researchers have found that the location and surrounding damages of lesions contribute more than the number and volume of lesions (Lipp et al., 2020). Accurate anatomical localization of affected tracts is also essential to understand the symptomatology, disease evolution, and intervention effects (Barkhof, 1999; 2002; Barkhof et al., 2009; Charil et al., 2003; Kolind et al., 2012; Lin et al., 2005). However, traditional voxel-based analysis of brain white matter is usually performed in a standard space and seems sensitive to registration error (Colby et al., 2012b). Therefore, tractography in native space becomes suitable for MS patients because it is free of registration and allows inter-subject variability of tract location and shape (Lipp et al., 2020). Since the pathological lesions of MS hinder basic tract reconstruction, clinical studies frequently employ advanced tractography methods to reconstruct individual tract streamlines (Sbardella et al., 2013) and obtain feasible results even when brain lesions are present (Lipp et al., 2020). After segmenting a tract of interest, specific dMRI metrics can be estimated within the tract (as described in Section 5.2). Tractography studies in MS have found that decreased FA or increased MD value in specific tracts, such as the corticospinal tract, the corpus callosum and cerebellar peduncles, are related to individual motor disabilities (Anderson et al., 2011; Kern et al., 2011; Lin et al., 2005; Wilson et al., 2003) and longitudinal changes of diffusion metrics of these tracts in patients are associated with the rehabilitation of motor function during training (Filippi et al., 2019; Prosperini et al., 2014). Importantly, quantitative tractography analysis in MS further highlights that

white matter tracts exhibiting normal appearance are also affected pathologically (Droby et al., 2015; Fleischer et al., 2019) and may be influenced by different pathological factors such as iron or myelin (Fang et al., 2019). The FA abnormalities in these tracts are found to be significantly correlated with cognitive abilities in pediatric patients at the early phase of the disease (Sbardella et al., 2013). These individual tract-based quantitative metrics are also promising in early clinical trials. For instance, researchers may use this approach to study specific rehabilitation interventions within relevant white matter tracts (Bonzano et al., 2014). By combining along-tract analysis and intra-cortical measurements, researchers further found that although the abnormalities in white matter tracts of MS are concomitant with intra-cortical injuries, this relationship is not strictly following a tract-cortex-specific pattern (Louapre et al., 2016).

MS is considered to be a typical disconnection syndrome due to the massive lesions observed (Rocca et al., 2015). Researchers have observed consistent disrupted network integration including reduction of global efficiency and network strength (Liu et al., 2018; Schiavi et al., 2020b; Shu et al., 2016; 2011), breakdown of long-range connections that account for remote communication (Muthuraman et al., 2016), decreased frontal network communicability that represents the parallel communication capacity (Li et al., 2013) and impairments of rich-club connectivity that serve as core highways (Shu et al., 2018a) in MS patients compared with healthy controls. Meanwhile, studies find increased clustering and modular connectivity patterns at 6 and 12 months after the first clinical event, which indicates a disease-related abnormality of network segregation ability (Fleischer et al., 2017; Muthuraman et al., 2016). Addressing such topological network abnormalities in MS benefits the tracking of high-level behavior disruptions and complex disease state at individual level. The disruption of structural networks is associated with impaired cognitive performance, especially involving attention and executive function (Llufriu et al., 2017). The decrease in global efficiency is significantly correlated with Expanded Disability Status Scale (EDSS) scores and disease duration (Shu et al., 2011). Researchers have further used network metrics to differentiate clinical subtypes of MS and achieved promising accuracy (Kocevar et al., 2016).

6.3.2. Schizophrenia—Schizophrenia has been considered to be a dysconnectivity disorder with a complex nature since the late 19th century (Collin et al., 2016; Goldsmith et al., 2018). Modern tractography techniques provide *in vivo* evidence for this hypothesis, indicating that schizophrenia may be seen in terms of affected pathways between cortical regions (Goldsmith et al., 2018; Griffa et al., 2013). For instance, the corpus callosum exhibits impairments of decreased FA in anatomical subdivisions in schizophrenia. These impairments are found reproducible across studies (Ohoshi et al., 2019; Price et al., 2007; Shahab et al., 2018) and are predictive for multiple cognitive domains (Sui et al., 2018) in both health and patients across datasets. A general question about schizophrenia is whether it is a disorder of whole brain dysfunction or one of selectively affected neural systems (Fornito et al., 2017). Studies frequently find consistent decreases of FA in tracts among fronto-temporal systems such as the superior/inferior longitudinal fasciculi, uncinate fasciculi, arcuate fasciculi, and cingulum bundles (Peters and Karlsgodt, 2015; Wheeler and Voineskos, 2014) in both chronic and first episode schizophrenia patients.

These tract-specific impairments exhibit significant symptom associations in deficits of working memory (Karlsgodt et al., 2008), hallucinations (Shergill et al., 2007) and attention (Abdolalizadeh et al., 2020). However, increasing evidence suggests that the impairments of tracts in schizophrenia are more widespread than classical frontotemporal regions (Fitzsimmons et al., 2013; Kelly et al., 2018; Klauser et al., 2017; Mamah et al., 2019; Zalesky et al., 2011), which emphasizes the need for whole brain investigation. There is evidence that tractography analysis showed higher specificity and sensitivity for detecting white matter impairments in schizophrenia, compared to the voxel-based analysis approach (Kanaan et al., 2006). Meanwhile, by combining along-tract profiles of whole brain fiber pathways (which cannot be obtained by voxel-based analysis) with an unsupervised clustering framework, researchers were able to identify biologically defined subtypes of schizophrenia rather than symptom-based divisions, which shows great promise for future studies (Sun et al., 2015).

Using the graph-theoretical framework (as described in 5.6), structural connectome studies (Collin et al., 2016; Fornito et al., 2017) have shown altered global network topology such as reduced network efficiency and increased characteristic path length in chronic (van den Heuvel et al., 2010; Wheeler and Voineskos, 2014; Zalesky et al., 2011) or first episode patients (Zhang et al., 2015), unaffected siblings (Collin et al., 2014b) and high-risk infants (Shi et al., 2012), compared with healthy controls. These results support that the impaired network integration may be foundational to schizophrenia's etiology and possibly reflect genetic vulnerability. Meanwhile, the disproportionate deficits of long-distance association edges, disruptions of anatomical brain hubs and rich club connections (Collin et al., 2014a; Crossley et al., 2017; Klauser et al., 2017; Van Den Heuvel et al., 2013; Yeo et al., 2016) in both patients and their unaffected siblings also suggest damage of topological infrastructures for inter-domain functional integration in schizophrenia (Collin et al., 2016). Studies also find evidence of abnormally enhanced network segregation such as increased modularity in schizophrenia patients and individuals with high-risk syndrome (Schmidt et al., 2017; Van Den Heuvel et al., 2013). These deficiencies of network topology are generally associated with the cognitive impairments and treatment responses during disease. The reduced global efficiency of patients is correlated with Positive and Negative Syndrome Scale (PANSS) scores (Wang et al., 2012) while higher global efficiency trend to be found in first-onset patients who subsequently respond to treatment, compared to non-responders (Crossley et al., 2017). The disruption of rich-club organization is also associated with PANSS scores and shows potential for classification between schizophrenia patients and healthy controls (Cui et al., 2019; Zhao et al., 2017b). Tractography-based networks are also a valuable framework to enable cross-species comparisons for pathogenesis; for instance, by comparing brain network connectivity between humans and chimpanzees, researchers find evidence of evolutionary modifications of human white matter connectivity to significantly overlap with the cortical pattern of schizophrenia-related dysconnectivity (Van Den Heuvel et al., 2019).

6.4. Tractography in neurosurgery

For neurosurgeons, *in vivo* tractography is invaluable for the planning and implementation of surgery, allowing for the visualization and localization of white matter tracts that are displaced or otherwise affected by the tumor (Jellison et al., 2004; O'Donnell et al., 2017).

Although there remain technical considerations (Essayed et al., 2017), in-vivo tractography offers essential spatial information about individual anatomical pathways for brain surgery planning and implementation (though quantitative metrics of local tracts are relatively less used in clinical care) in the fields of lesion resection and deep brain stimulation (DBS).

During tumor resection surgeries, *in-vivo* tractography, especially in intraoperative MRI, allows for the accurate visualization and localization of white matter tracts that are displaced or affected by tumors (Chen et al., 2016a; Jellison et al., 2004), which is important for the quality of life and overall survival of neurosurgical patients (Costabile et al., 2019; Essayed et al., 2017; Fortin et al., 2012; Panesar et al., 2019). In neoplastic lesion surgery, balancing the trade-off between function preservation and maximized resection is highly significant. The classical gold standard is the intraoperative identification of eloquent areas by direct electrical stimulation (DES) (Duffau, 2005; 2015; Essayed et al., 2017; Szelényi et al., 2010). Recent applications of *in vivo* tractography from intraoperative MRI have shown a relatively high correlation between distances to reconstructed tracts and positive DES intensities (Essayed et al., 2017). Using intraoperative MRI has also shown to provide a more comprehensive surgical white matter mapping by identifying fiber tracts that were not detected in preoperative tractography (Javadi et al., 2017). Studies have shown that when combined with navigated transcranial magnetic stimulation (nTMS), intraoperative tractography aids in preserving speech for patients with tumors adjacent to the superior longitudinal fasciculus (Negwer et al., 2017; Sollmann et al., 2018). Additionally, in language area surgery, when awake surgery is impossible or unavailable, tractography-based estimation may become the only available solution for assessing involved white matter tracts (D'Andrea et al., 2016). The applications of *in vivo* tractography have been widely used in various lesions located in both supratentorial and infratentorial areas (Ellis et al., 2012; Fernandes-Cabral et al., 2016; Kovanlikaya et al., 2011), involving not only the major tracts but also smaller fiber structures (Meola et al., 2016).

In psychiatric surgery, tractography results are used to improve targeting during DBS surgery for patients with refractory psychiatric diseases such as depression, obsessive-compulsive disorder (OCD), or posttraumatic stress disorder (PTSD) (Davidson et al., 2020; Fenoy, 2020). For instance, the ventral tegmental area projection pathway (VTApp), which is the potential target of stimulation in many translational cases during psychiatric DBS, cannot be appreciated on standard structural MRI images. In-vivo tractography can be used to maximize the contact with the VTApp of stimulation electrode by optimizing the invasive depth and trajectory after the visualization of fiber streamlines (Coenen et al., 2019; Davidson et al., 2020; Schlaepfer et al., 2013). Such a DBS approach brings rapid improvements on clinical responses and remissions in several open-label trials, although it needs to be further studied through large randomized trials (Coenen et al., 2019). Similar efforts have also been pursued for major targets including the subcallosal cingulum (SCC) and ventral capsule/ventral striatum (VC/VS) in clinical practice (For a review, see Davidson et al., 2020).

The brain connectomic concept benefits traditional surgical strategy by a potential shift from focusing on local topography to a network-guided "oncological disconnection surgery" (Duffau, 2021; Hart et al., 2020). In a classical neurosurgical view, the inflexible definition

of “eloquent” brain regions represented by the sensorimotor, language and visual cortices serves as an irrefutable principle: tumors involving “eloquent” cortex would not be selected for resection while tumors locating in “non-eloquent” areas could be operated without considerations (Spetzler and Martin, 1986). However, considering the potential for functional compensation and the presence of individual variation, a common location of “eloquent” areas across patients seems inaccurate (Southwell et al., 2017). By combining tractography atlases with intraoperative electrical stimulation for functional mapping, researchers have constructed probabilistic atlases of white matter pathways and structural hubs that define a minimal common brain connectome with a low inter-individual variability and a low potential of post-lesional compensation (Herbet et al., 2016; Sarubbo et al., 2020). Such prior “structural and functional skeletons” provide a whole brain knowledge map of essential brain sub-networks, which may be helpful in informing the resection of certain neuronal circuits during tumor surgery (Duffau, 2021). For instance, connectomic studies have shown that the lexical access speed, which is related to the return to professional work after awake surgery for patients with low-grade gliomas, may be completely disrupted only when the left inferior longitudinal fasciculus (ILF) is damaged (Moritz-Gasser et al., 2012). An elaborate surgical management can now take into account the white matter circuits involved with functional reconfiguration that affected by tumors/lesion (Van Horn et al., 2012). Researchers also have tried to develop a “connectomic risk signature” for lesion surgery using brain function simulation based on tractography results (Aerts et al., 2018). In this study, the authors employed neural dynamic models on empirical tractography data of a cohort of patients with gliomas and meningiomas to create a virtual brain functional network and observed distinct individual signatures depending whether the brain regions were directly affected by tumors. In psychiatric surgery, advanced tractography facilitates the combination between brain connectomic analyses and neuromodulation interventions (Davidson et al., 2020; Horn et al., 2017; Riva-Posse et al., 2018), which fuels the emerging concept of “Connectomic DBS” (Baldermann et al., 2021; Horn and Fox, 2020). This simulation approach aims to modulate an optimal interconnected network instead of targeting local sites. It may partly reduce the ambiguity about the best intervention target and is quite suitable for brain disorders that involve several abnormal circuits, e.g., OCD (For a review, see (Baldermann et al., 2021)). Furthermore, connectomic neuromodulation may contribute to identifying specific networks that lead to symptom-specific treatments, paving the way for personalized therapy (Horn and Fox, 2020). For instance, in Parkinson’s disease, researchers found that DBS on sub-thalamic nucleus linking to the supplementary motor area is associated with improvement in bradykinesia and rigidity, while DBS on nucleus structurally commenting to M1 is associated with improvement in tremor (Akram et al., 2017). These studies indicate the potential of using individual quantitative tractography to generate neurosurgical prognostic markers at the brain system level in the future.

7. Discussion and conclusion

In this review paper, we have provided a high-level overview of how tractography can be used to enable quantitative analysis of the brain’s structural connectivity in health and disease. We reviewed methods that are involved in the main processing steps for quantitative

analysis of tractography. We also reviewed studies that have used quantitative tractography to study the brain's white matter.

For research and clinical applications using tractography, we note that researchers should be extremely cautious when making biological interpretations about quantitative results. The reconstructed streamlines are only simulated entities that do not correspond directly to nerve fibers (Jeurissen et al., 2019; Yeh et al., 2020), and basic diffusion metrics are only inferences based on local diffusion properties, which are not direct measures of tissue properties (Assaf et al., 2019). Multiple review papers illustrate pitfalls to be avoided when performing quantitative dMRI analysis and studying the brains connectivity using tractography (Daducci et al., 2016; Jones, 2010; O'Donnell and Pasternak, 2015; Rheault et al., 2020c). Research is underway to improve biological specificity to the type of tissue change, by improving the information that is obtained at the acquisition level (Barakovic et al., 2021a; Henriques et al., 2020; Hutter et al., 2018; Ning et al., 2019; Shemesh et al., 2016; Westin et al., 2016), and by proposing advanced mathematical modeling and machine learning techniques (Nath et al., 2021; Ning et al., 2021; Pizzolato et al., 2020; Wu and Miller, 2017).

The anatomical accuracy of tractography is an ongoing issue in quantitative tractography analysis, where both false positive and false negative tractography results pose challenges (Maier-Hein et al., 2017; Thomas et al., 2014). While technical improvements (e.g., using fiber filtering techniques as introduced in Section 3.5) can improve anatomical accuracy, researchers should be cautious when interpreting results in research and clinical applications by considering prior anatomical knowledge learned from studies in histology (Huttenlocher, 1984; Miller et al., 2012; Sidman and Rakic, 1973; Yakovlev and Lecours, 1967) and animals (Song et al., 2003; 2002).

Tractography has enabled the study of the brain's white matter connections across the lifespan in health and disease. Overall, we conclude that, while there have been considerable advancements in methodological technologies and breadth of applications, there nevertheless remains no consensus about the "best" methodology in quantitative analysis of tractography, and researchers should remain cautious when interpreting results in research and clinical applications.

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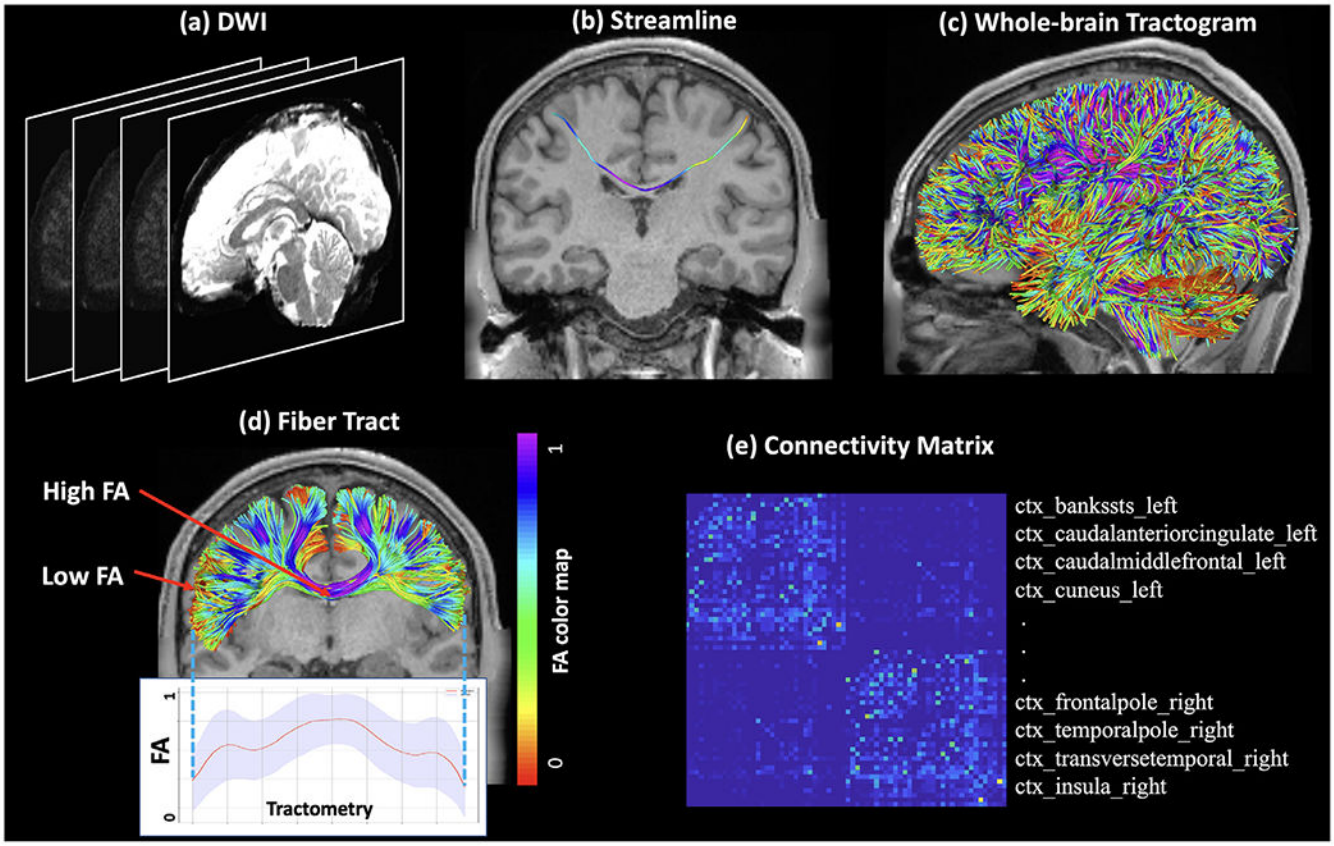

Fig. 1.

Graphic illustration of tractography. (a) Example dMRI data, also known as diffusion weighted imaging (DWI) data. (b) An individual streamline computed after performing tractography. (c) An example whole-brain tractogram that consists of streamlines covering the entire white matter. (d) A fiber bundle that consists of a set of streamlines, representing an anatomical fiber tract named the corpus callosum. The streamlines are colored by a microstructural measure, i.e., fractional anisotropy (FA) that measures the anisotropy of water diffusion. The distribution of FA along the fiber tract is provided to show the tractometry of the tract. A low FA can be seen at the endpoint region of the streamlines (near the cortex) and a high FA can be seen in the middle of the streamlines (in the deep white matter). (e) An example brain structural connectivity matrix, which is constructed based on white matter tractography from the whole brain. Each row (and column) represents a brain gray matter ROI (See Fig. 3(c) for an example brain gray matter parcellation), and the value in an element of the matrix is the strength of the white matter connection between the two corresponding ROIs (quantified as the number of streamlines in this case).

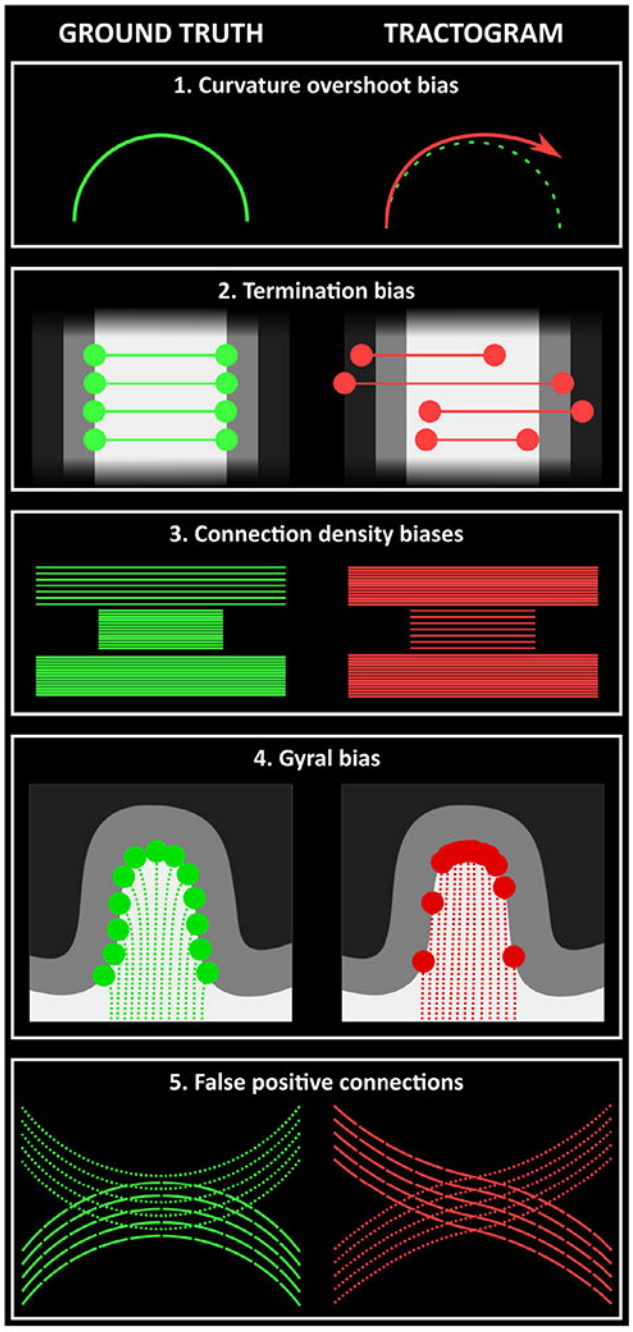

Fig. 2.

Demonstrations of various forms of errors and biases in tractography, as described in Section 3. Images are exemplars only; therefore there exist many other possible manifestations of such biases and errors. 1. Low-order integration methods under-estimate bundle curvature, leading to reconstructed paths overshooting the underlying curved trajectory. 2. In the absence of tailored constraints, streamlines may terminate in locations other than those known to contain axon synapses. 3. The number of streamlines generated within a bundle may not be proportional to the underlying axonal density of that bundle. 4. Because of the

low resolution of diffusion MRI relative to the complexity of gyral folding, streamline termination may accumulate at gyral crowns rather than being distributed uniformly across the cortical ribbon. 5. Where macroscopic WM bundles intersect, streamlines may erroneously traverse part of one bundle and part of another, producing trajectories that are not present in the underlying structure (Schilling et al., 2021).

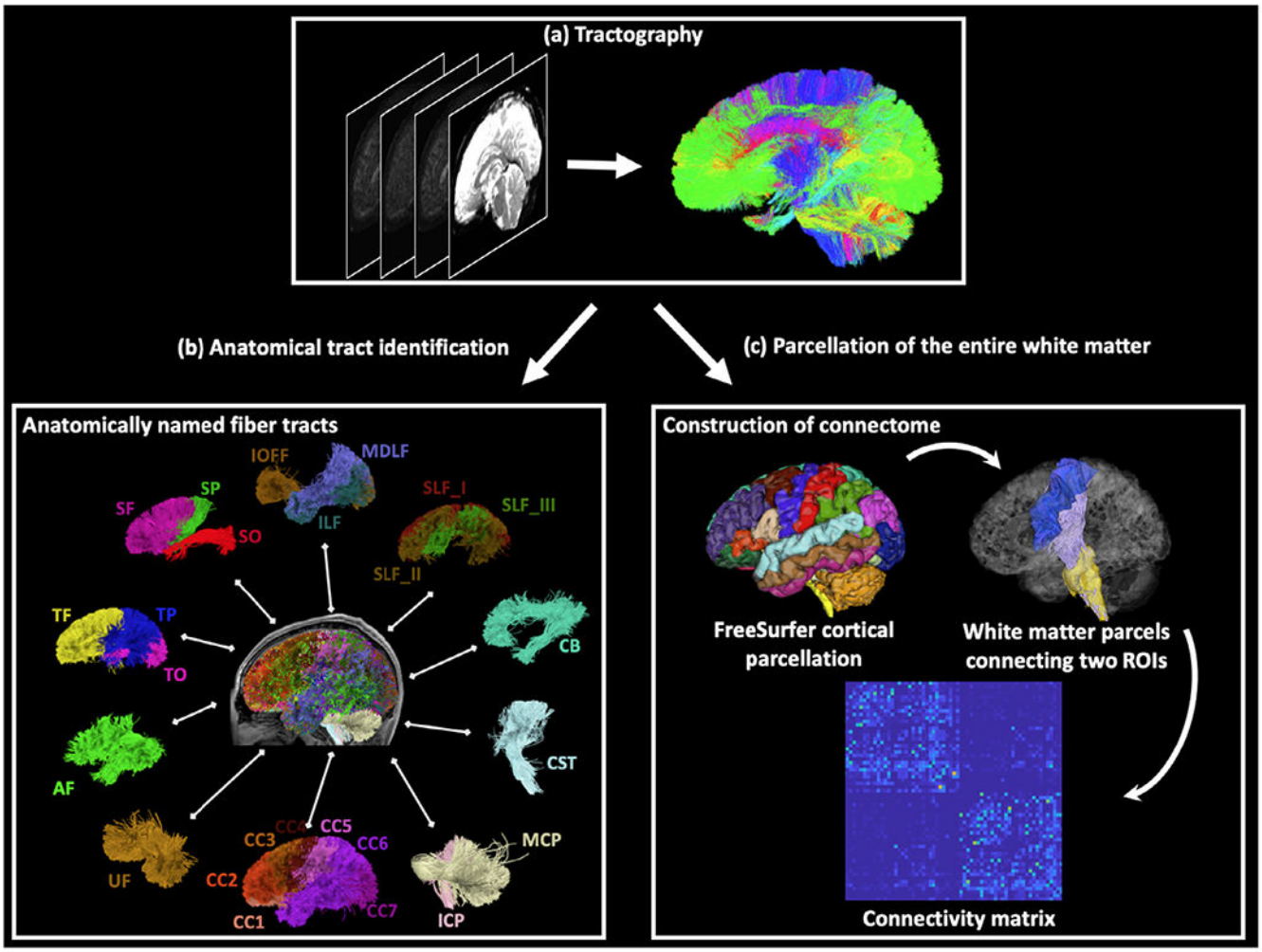

Fig. 3.

Tractography segmentation: (a) Example whole-brain tractogram computed by performing tractography in DWI data; (b) Example anatomical tracts extracted from the tractogram; and (c) Example structural connectivity matrix constructed by performing whole brain tractography segmentation between all pairs of FreeSurfer cortical regions.

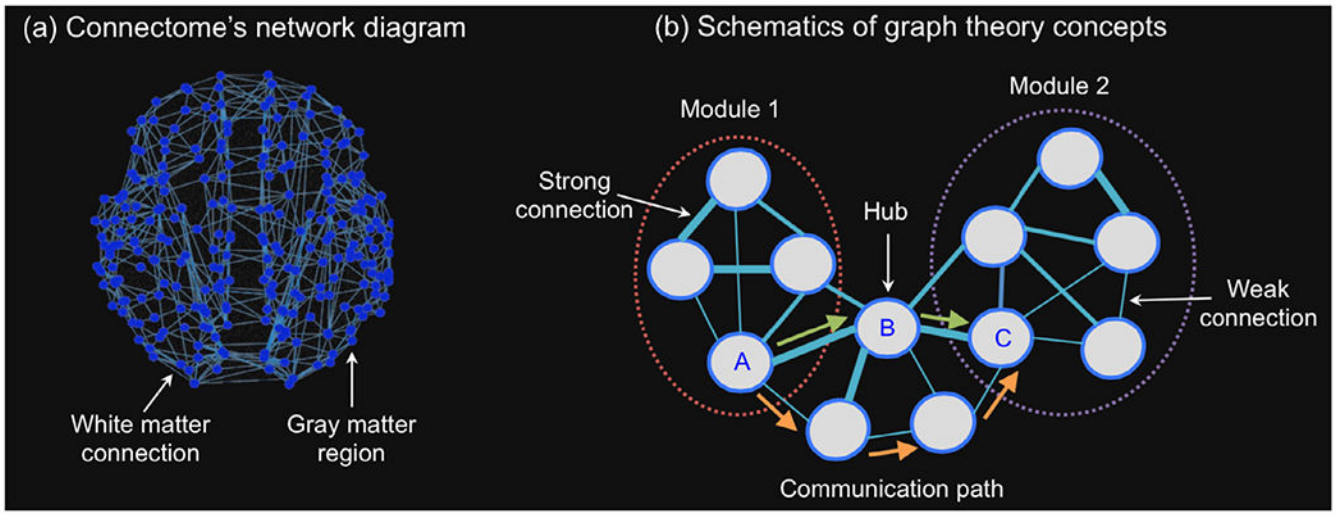

Fig. 4.

Graph theoretical analysis of the human connectome. (a) Network diagram of structural connectivity, where nodes represent gray matter ROIs and connections depict white matter fiber bundles. (b) Schematics of key graph theory concepts applied to the analysis of structural connectivity. The thickness of connections indicates the strength of structural connectivity between two ROIs (e.g., NOS or integrated FA). Region-level graph measures such as degree, strength, and centrality identify ROI B as an important hub in the network. At the mesocale, two modules or communities are observed. Intra-module connectivity is dense and inter-module connectivity in sparse. At the global scale, communication paths delineate multi-step sequences linking anatomically unconnected ROIs. Two possible paths connecting ROIs A and C are highlighted in green (shortest path) and orange (alternative path).

Table 1

Common terms used throughout this paper and their definitions. We note that there are traditional terms that are widely used, but are not technically or biologically precise; in this table, we emphasize such terms and encourage the avoidance of their usage in future studies.

Term	Definition
Tractography / Fiber tracking	Any computational process that estimates the anatomical trajectories of the white matter fiber pathways from dMRI data. *Note*: The term "Fiber tracing" and "Fiber tracking" are also widely used. However, we strongly suggest avoiding this term because "tracing" is frequently used in the context of *ex vivo* tracer injections, and "tracking" refers to following a moving object while white matter fibers do not move.
Streamline	A set of ordered points in 3D space, encoding a trajectory estimated through performing tractography (see Fig. 1(b)). *Note*: The term "fiber " is also widely used. However, we strongly suggest avoiding this term because "fiber" is in reference to biology, while "streamline" implies the digital reconstruction of such.
Tractogram	A set of streamlines, often generated in such a way as to cover the entire white matter of the brain in order to capture any possible white matter connections. This can be referred to as a "whole-brain tractogram" (see Fig. 1(c)).
Steamline cluster/ Streamline connection/ Streamlines within an edge/ White matter parcel	A set of streamlines resulting from the subdivision of a tractogram. Such sets can result from a variety of methods for dividing the tractogram; hence there are several names in use for them. While such a set is often called a "fiber bundle," "fiber tract," or "fiber cluster" in the literature, to clarify that a set of streamlines is a computational data representation, we avoid using the word "fiber" in this paper.
Fiber Bundle / Fiber Tract / Fiber Fasciculus / Fiber Pathway	These terms have biological meanings as a set of white matter fibers (axons) forming a corticocortical or corticosubcortical connection in the brain (Schmahmann, Schmahmann, Pandya, 2009). In the neuroimaging literature, these terms are commonly used *instead* to refer to white matter connections reconstructed using tractography. Following this practice, in this paper we will use the terms "fiber tract," "fiber bundle," "fiber fasciculus," or "fiber pathway" to refer to a white matter structure that corresponds to known anatomy with a traditional name (e.g., the corpus callosum or the corticospinal tract) (see Fig. 1(d)).
Brain Connectivity	In neuroimaging, the somewhat elusive and ambiguous concept of brain connectivity refers to measures of the structural and/or functional relationship between different brain regions (Horwitz, 2003; Rossini et al., 2019; Sakkalis, 2011; Uddin, 2013).
Structural Connectivity	A specific type of brain connectivity. Two brain regions are structurally connected if a fiber tract physically interconnects them. This is typically measured *in vivo* in humans using dMRI. However, there is no consensus on how this should be best quantified. Structural connectivity measures (also called "weights" or "strengths") can include a variety of quantitative connectivity measures computed from a specific set of streamlines corresponding to a pathway of interest (e.g. those connecting two specific endpoints). The goal is often to approximate the true underlying fiber density or number of axons (Jones, 2010; Smith et al., 2020a).
Connectome / Brain Connectivity Matrix	A two-dimensional matrix wherein the rows and columns correspond to specific brain gray matter regions of interest (ROIs), and the value stored within each element of the matrix is the computed connectivity " strength" between those regions corresponding to that row & column (Sporns, Tononi, Kötter, 2005) (see Fig. 1(e)). Such data are described mathematically as a graph. This matrix representation is directly inspired by invasive axonal tract-tracing experiments in animals, where the results of multiple studies are expressed as a quantitative connectivity matrix (Wakker et al., 2012). Without further specification, we use "connectome" throughout to implicitly refer to the *structural* connectome constructed using dMRI tractography, as opposed to those derived through other imaging modalities (e.g., functional MRI).
Diffusion Model	A theoretical model that connects the dMRI signal to salient features of tissue microstructure at the cellular level (Novikov et al., 2018; Panagiotaki et al., 2012; Yablonskiy and Sukstanskii, 2010). This includes tissue microstructure or biophysical models such as Neurite Orientation Dispersion and Density Imaging (NODDI) (Zhang et al., 2012) and Free Water (FW) (Pasternak et al., 2012, 2009, as well as diffusion signal representations that include the diffusion tensor (Basser and Pierpaoli, 1996), diffusion kurtosis (Jensen and Helpern, 2010) and many others (Afzali et al., 2020; Alexander, 2006).
Microstructural Measure	Any parameter extracted from a diffusion model fit in each voxel that provides information regarding the underlying tissue microstructure (e.g., the fractional anisotropy (FA) that describes water diffusion anisotropy (Basser and Pierpaoli, 2011)).
Tractometry / Profilometry / Tract-based morphometry	An along-tract profiling analysis technique to investigate the distribution of the microstructural measures along the fiber pathway (Bells et al., 2011b; O'Donnell et al., 2009; Yeatman et al., 2012).