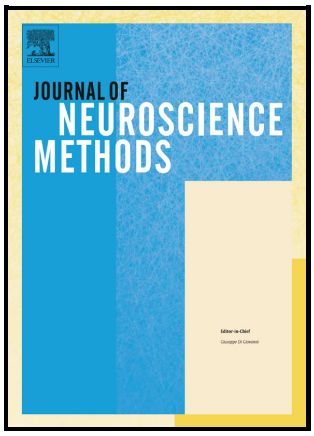

A methodological scoping review of the integration of fMRI to guide dMRI tractography. What has been done and what can be improved; a 20-year perspective

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Manuscript

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Abstract
Combining MRI modalities is a growing trend in neurosciences. It provides opportunities to investigate the brain architecture supporting cognitive functions. Integrating fMRI activation to guide dMRI tractography offers potential advantages over standard tractography methods. A quick glimpse of the literature on this topic reveals that this technique is challenging, and no consensus or "best practices" currently exist, at least not within a single document. We present the first attempt to systematically analyze and summarize the literature of 80 studies that integrated task-based fMRI results to guide tractography, over the last two decades. We report 19 findings that cover challenges related to sample size, microstructure modelling, seeding methods, multimodal space registration, false negatives/positives, specificity/validity, gray/white matter interface and more. These findings will help the scientific community (1) understand the strengths and limitations of the approaches, (2) design studies using this integrative framework, and (3) motivate researchers to fill the gaps identified. We provide references toward best practices, in order to improve the overall result's replicability, sensitivity, specificity, and validity.

Keywords:
Functional MRI, tractography, diffusion MRI, multimodal neuroimaging, scoping review

Introduction

The combination of functional MRI and diffusion MRI

MRI is sometimes compared to a "Swiss knife" because it is a single tool that has multiple functions. Thus, MRI is a perfect means by which to collect multimodal brain imaging data; it can be used to collect information about the brain's anatomy (structural MRI [sMRI]), activity (fMRI), and to probe white matter organization and microstructural properties (diffusion MRI [dMRI]). Acquiring multimodal brain data in a

single study is common practice, yet most scientific investigations tend to analyze and report their results in a unimodal or separated fashion (Calhoun and Adali, 2009; Sui et al., 2014). However, the combination of fMRI and dMRI data to study brain activations and white matter, respectively, is a growing trend (Soares et al., 2013). This multimodal approach is strongly encouraged by the cognitive neuroscience research community in order to better understand the brain architecture that sustains cognitive functions (Calamante et al., 2013; Zhu et al., 2014). The combination of multimodal MRI data can shed light on the anatomical and functional organization of the brain, and improve our understanding of many brain phenomena (i.e., development, cognition, pathological processes, and psychiatric disorders) (Sui et al., 2014).

MRI modalities

Functional MRI (fMRI)

Functional MRI has contributed to critical progress in the field of cognitive neuroscience. Task-based fMRI allows identification of the patterns of neural activation associated with an experimental task. It relies on the measurement of dynamic changes in brain oxygenation levels (BOLD signal) due to underlying neuronal activity (Chen and Glover, 2015). FMRI is also used to investigate the brain's BOLD signal spontaneous fluctuation when at rest (Biswal et al., 1995; Fox et al., 2005; Raichle and Mintun, 2006). Resting state fMRI (rs-fMRI) relies on the assumption that brain regions maintain temporally synchronized patterns of spontaneous activity, in an organized fashion, that forms interconnected networks such as the Default Mode Network (Greicius et al., 2003; Raichle and Mintun, 2006). The recent development of fMRI connectivity analysis has provided new ways to investigate the relationship between active brain regions, by measuring their connectivity (i.e., functional and effective connectivity) (Friston, 2011).

Diffusion MRI

dMRI pledges to help us in our understanding of the brain's white matter organization. By probing the diffusion of water molecules in the brain, dMRI provides useful information about the underlying microstructural properties of white matter (Jones, 2010a). The diffusion of water molecules is highly dependent on their immediate surrounding environment. White matter is mostly composed of densely packed and organized axons, oligodendrocytes (myelin sheaths), and other glial cells, where the random motion of water molecules becomes restricted and hindered, which strengthen the dMRI signal. In contrast to white matter, water molecules diffuse freely in the cerebrospinal fluid, resulting in a dMRI signal loss. The behavior of water molecules in gray matter lies somewhere between that of cerebrospinal fluid and white matter. Indeed, gray matter is composed of neuronal cell bodies, dendrites, and glial cells that allow some degree of free diffusion and some degree of restricted and hindered diffusion (intermediate signal) (Rowe et al., 2016). Different microstructure modeling strategies have been proposed in the last decades in order to better understand the complex organization of the local microstructure of tissues probed by dMRI. Models include diffusion tensor imaging (DTI) (Basser et al., 1994), Q-ball imaging (Tuch, 2004), spherical deconvolution (SD) (Tournier, Calamante, Gadian, & Connelly, 2004), amongst others, and each have their own strengths and weaknesses (see Descoteaux & Poupon, 2012 for a review). These dMRI local microstructure models allow two main types of analysis. The first type is voxel-based analysis of white matter microstructural properties, such as fractional anisotropy (FA) or other metrics (e.g., axial diffusivity [AD], radial diffusivity [RD], and mean diffusivity [MD]). This analysis can be carried out using a standard parametric voxel-based approach, or by using alternatives such as tract-based spatial statistics (TBSS) (Jones and Cercignani, 2010; Smith et al., 2006; Van Hecke et al., 2016). The second approach, tractography is a computational approach attempting to virtually reconstruct white matter structural pathways (Caan, 2016; Descoteaux and Poupon, 2012). Thus, both

approaches, voxel-based and tractography, allows the analysis of the same white matter microstructural properties. However, one happens at the voxel level, while the other, tractography, encompasses the whole course of the reconstructed streamlines, or subparts of it (see 'tractometry' and 'tract profiling' in Boukadi et al., 2019; Cousineau et al., 2016; Yeatman et al., 2012.

Before the advent of tractography, we had to rely solely on more invasive means, such as animal tracer studies, Wallerian degeneration, myelogenic development and post-mortem human brain dissection to investigate white matter pathways (Axer, 2011; Axer et al., 2013; Catani et al., 2002; Chanraud et al., 2010; Schmahmann and Pandya, 2006). Tractography allows the course of white matter fiber bundles to be followed between two (or more) selected brain regions, which can be validated with other more invasive methods (Catani, 2010; Catani et al., 2002; Wakana et al., 2004). Tractography also provides information about in-vivo neuroanatomical connections between brain regions (structural connectivity) and white matter microstructural properties (Caan, 2016; Jones, 2010a). However, the methods used to quantify structural connectivity should be used with caution because they remain the subject of vigorous scientific debate (Calamante, 2019; Jones, 2010b; Jones et al., 2013; Maier-Hein et al., 2017). The integration of fMRI to guide tractography represents an excellent means by which to gain insight about the functional and structural organization of cognitive brain functions. For this reason, our scoping review will focus on the integration of fMRI task-related brain activations to guide tractography, rather than dMRI voxel-based analysis (i.e., TBSS).

Types of combination

Overlay approaches

Thus far, a growing number of studies combine fMRI and dMRI data with different methodological approaches. One can collect functional and diffusion data and analyze these in a parallel way. This is defined as an overlay approach (Calhoun and Adali, 2009; Sui et al., 2014) because results from multiple MRI modalities are simply co-registered (i.e., in native space), or normalized in a common template (group-wise analysis), but do not interact with one another and remain independent (see Figure 1A). The reader can find examples of the overlay approach in: Cha et al., 2016; Chamberland et al., 2017; Papadelis et al., 2014; Perobelli et al., 2015; Santhanam et al., 2011; and Sun et al., 2018. Note that it is also possible to compare structural connectivity matrices with functional connectivity matrices obtained from fMRI (Horn et al., 2014).

Data fusion approaches

Another way of combining multiple MRI modalities is data fusion. This is a symmetric approach where multiple MRI modalities (i.e., fMRI and dMRI) contribute to the same statistical model to identify how these fused data sets explain a phenomenon of interest (Calhoun and Adali, 2009; Sui et al., 2014) (see Figure 1B). Data fusion involves exploratory analysis such as joint independent component analysis (jICA). The reader can find examples of data fusion in: Calhoun, Liu, & Adali, 2009; Franco et al., 2008; Sui et al., 2012, 2013, 2011; and Teipel et al., 2010.

Data integration approaches

Conversely, data integration is an asymmetric approach where one modality is used to enhance or constrain the second one (Sui et al., 2014) (see Figure 1C). An example of such an integrative multimodal MRI approach is when fMRI task-related brain activations are used to precisely guide the tracking of the white matter fiber bundle via dMRI tractography (also referred to as 'fiber tracking') (Bernier et al., 2014; Caan, 2016; Descoteaux and Poupon, 2012). Note that this precision will depend upon the implementation of the procedure and the quality of the data and its critical examination is one of the objectives of this scoping review. The

opposite approach is also possible (i.e., functional connectivity guided by dMRI tractography), as demonstrated in Chamberland et al., 2015. Since cognitive functions are implemented through large-scale brain networks, the integration of fMRI and dMRI data is an exciting approach to disentangle the neural organization of mental processes in the brain (Catani and Ffytche, 2005; Mesulam, 1990; Sui et al., 2014). For this reason, multiple articles using this integrative framework will be presented in this scoping review.

Advantages of the integration of fMRI to tractography

When multimodal brain datasets that comprise fMRI and dMRI are available, the integration of fMRI to guide tractography offers potential advantages over the standard dMRI tractography methods. In previous studies, two principal methods were commonly used to perform dMRI tractography. One requires the initial definition of seed regions based on anatomical landmarks from brain atlases, or the reliance on manual seed placement on directionally encoded color fractional anisotropy maps (DEC-FA maps). The second firstly performs whole-brain tractography by seeding every voxel in the white matter (or the gray and white matter interface), with a pre-defined ending criteria (e.g., gray matter), and then filters out the tracts of interest that intersect the regions of interest obtained from a chosen brain atlas (Descoteaux and Poupon, 2012; Girard et al., 2014; Soares et al., 2013; St-Onge et al., 2018). The latter method suffers from limitations, as the following are sometimes assumed:

1. The entire selected brain regions are involved in the process of interest, which is sometimes true, however, sub-parts of a given brain region can be involved in more specific processes (Yang et al., 2009)
2. The brain anatomical and functional organization is not deformed by a pathological entity (i.e., tumor) (Niu et al., 2016; Schonberg et al., 2006; Uzuki et al., 2009)
3. The analyzed brains developed in a typical manner, which may not the case in many neurodevelopmental disorders
4. The analyzed brains are at the same level of development/maturation as the atlas of reference, which can be problematic when studying pediatric or elderly populations (Broser et al., 2012)

The manual placement of seed regions in DEC-FA maps is 1) user and expertise dependent, which makes it error-prone; and 2) depends on the chosen DTI atlas and the chosen tract delineation guidelines (Lee et al., 2012). Furthermore, studies have shown that seed placement precision is critical because it influences the results of fiber tracking (Liu, 2011; Soares et al., 2013). Therefore, the seeding method derived from task-based fMRI results could enhance the precision of fiber tracking by targeting parts of the brain functionally involved in the sensory, motor, or cognitive process of interest, while respecting the subjects' or targeted groups' underlying functional and structural organization. In addition, this data integration approach allows, to a certain degree, interpretation of the relationship between specific white matter fiber tracks and a given cognitive process, a concept that some authors have termed as "functionally defined white matter" (Gomez et al., 2015). This is an argument that has motivated research groups to initiate their tractography based on fMRI experimental results. However, such claims must be made with caution, while respecting the limitations of each method (fMRI and dMRI) and incorporating a priori knowledge from other sources (e.g., brain stimulation studies, dissection studies, animals tracing studies, or evidence from neurological patients) (Duffau, 2008; Jones and Cercignani, 2010; Park and Friston, 2013; Raichle and Mintun, 2006; Schmahmann and Pandya, 2006). Finally, structural connectivity between brain regions active during a given cognitive process can be investigated when integrating fMRI experimental results to guide fiber tracking.

The arguments discussed above clearly highlight the potential relevance of integrating fMRI and tractography, although, as the saying goes, more is not always better. In their studies, Dyrba et al. showed that, in some instances, adding another MRI modality did not improve their classification accuracy of Alzheimer's disease patients (Dyrba et al., 2015). Even though this study used the data fusion approach, it serves as a proof of concept. Obviously, the decision to combine multiple MRI modalities must be clearly in line with the research questions and must result in the identification of new and useful information. A quick glimpse of the scientific literature relating to this topic has led us to believe that this technique is quite complex, that no guidelines or consensuses exist, and that it poses many challenges that are not clearly addressed by the current literature, or at least not within a single document. Consequently, there is a clear need to compile and summarize the literature on this precise topic.

Aims

Our aim was to review articles that integrated task-based fMRI results to guide dMRI tractography, in order to address the challenges that this new field of research faces, provide some solutions, and discuss the advantages and limitations of using this integrative approach. We restricted our analysis to the integration of task-based fMRI, without covering the integration of functional connectivity obtained by rs-fMRI. This was because 1) we were interested in using the integration of task-based fMRI in a research project and 2) the amount of articles to review would have been overwhelming if we had covered both types of fMRI analysis. However, it must be kept in mind that rs-fMRI results can be used to guide tractography (for examples see: Cui et al., 2017; Figley, Bhullar, Courtney, & Figley, 2015; Ge et al., 2013; and Palesi et al., 2016).

Methods

Since our topic is broad and has not yet been extensively reviewed, we opted for a scoping review approach because our research goals necessitate raking through a wide range of research topics. This approach is widely used in human sciences and allows for the synthesis of knowledge, the mapping of relevant key concepts, and the identification of gaps in a defined area where the patients'/participants' population characteristics, study designs, methods, and data analyses are heterogeneous (Arksey and O'Malley, 2005; Dijkers, 2011; Peters et al., 2015; Pham et al., 2014; Tricco et al., 2016). It is based on an exhaustive and systematic search of the literature based on key words. We adopted the five-stage framework for conducting a scoping review, as reported by Arksey and O'Malley (2005). This framework included the following five steps: (1) identifying the initial research questions, (2) identifying relevant studies, (3) study selection, (4) charting the data, and (5) summarizing and reporting the results.

(1) Identifying the initial research questions: Our goal was to compile and provide a descriptive and critical overview of the available experimental reports using task-based fMRI results to guide dMRI tractography. We will address the challenges that this new field of research faces, provide some solutions, and discuss the advantages and limitations of using this integrative approach.

Concerning the integration of task-based fMRI results to guide tractography, we aimed to address the following research questions and, when possible, sought to identify the associated advantages and limitations:

1. What type of combination approach is most widely used?
2. What sample size is commonly used when using this integrative approach?
3. Is it used to investigate a clinical population (if yes, which one)?
4. What are the commonly used dMRI acquisition parameters?

5. What packages or software is used to analyze MRI data in the reviewed articles?
6. What fiber tracking strategies and algorithm classes are used?
7. How are seed regions from task-based fMRI derived for tractography?
8. How do researchers deal with the gray and white matter interface when using the task-based fMRI seed region for guidance?
9. How do researchers deal with the different MRI modality (native or standard) spaces?
10. How do researchers present/report their results using this integrative approach?
11. Do researchers validate their fiber tracking results by triangulation?
12. When analyzing diffusion metrics along the obtained tracts, how is it done and do authors include a comparison/control tract?
13. Do authors label their fiber tracking results when using this integrative approach?

(2) Identifying relevant studies: First we conducted a documentary search using all the Web of Science databases. Since fMRI and dMRI were emerging in the 1990s, we thought it would be reasonable to only include studies published between January 1, 1990 and September 28, 2018. Second, we performed an update of the literature from October 2018 to august 2021.

We searched for the following keywords: [“fMRI” OR “Functional magnetic resonance imaging”] AND [“DTI” OR “tractography” OR "fiber tracking"] AND [“combin*” OR “multimodal”]. We included articles that reported primary experiments involving task-based fMRI brain activation to guide fiber tracking. We excluded case studies, non-human or post-mortem research, reviews, meta-analysis, and methodological papers. Publications in a language other than English were excluded because of the cost and time involved in translating the material. Note that we did not examine unpublished or ambiguous literature in our scoping review. For these reasons, important publications could have been neglected.

(3) Study selection: Before the literature update, we retrieved 643 results published between 1995 and September 2018 through the database search. Titles and abstracts were screened by one of the authors (JJ) according to the above-mentioned inclusion and exclusion criteria. A psychology undergraduate student with no formal training in MRI was trained by JJ to independently screen 10% of randomly selected titles and abstracts (N=64) for quality assurance. Inter-rater percent agreement was 90.62 % and reached 100% when disagreements were resolved. In the case of a considerable discrepancy between the two judges, we planned to invoke a systematic inter-rater procedure. However, this was not required. After the update, we retrieved another 161 results published between October 2018 and august 2021 leaving us with 804 articles from which two duplicates were removed and 14 other articles were added through cross-referencing. Out of these 816 articles that were screened a total of 736 articles were excluded for not meeting the inclusion/exclusion criteria or omitted for not containing enough information (i.e. proceedings and conferences abstracts). This left us with a final count of 80 articles to be included in the scoping review. Figure 2 shows a PRISMA flow diagram outlining our scoping review process (Moher et al., 2016; Peters et al., 2015)

(4) Data charting: For each article included in the scoping review, we extracted the following data: 1) year of publication; 2) name of the journal; 3) the neuroscience domain (e.g., language, perception, memory, and others); 4) sample size; 5) study population (healthy and/or clinical); 6) scanner strength; 7) fMRI design and experimental paradigm; 8) dMRI data acquisition parameter (b-values and number of gradient directions); 9) dMRI and fMRI processing/analysis software; 10) methods used to derive tractography seed region from task-based fMRI results; 11) analysis performed at the individual or group-wise level in the native or standardized

space; 12) methods used to insure contact between white matter and fMRI driven tractography seed regions; 13) dMRI models used (i.e., diffusion tensor or higher order); 14) fiber tracking algorithm class (i.e., deterministic or probabilistic); 15) track selection method (i.e., whole-brain tractography or seed-based); and 16) diffusion and tractography metrics analyzed (e.g., FA, AD, RD, track volume of length, number of streamlines, and others).

As our critical reading of the selected articles progressed, further questions gradually came to mind. Therefore, "new" data were extracted a posteriori to the initial research questions. These were 1) the presence of a reference from the scientific literature to cross validate the results of fiber tracking (e.g., an animal tracing study or human post-mortem dissection), 2) the presence of a control/comparison tract, 3) whether fMRI data was obtained from the same or different samples as the dMRI data, 4) which methods were used to perform the analysis of diffusion metrics on the obtained track (whole track mean or subparts of it), and 5) if the labeling of the fiber tracking result was in accordance with a known white matter structure (e.g., as depicted in a brain atlas).

We directly addressed questions about the article to the corresponding author, by e-mail, when we needed clarification about a topic during our critical reading.

(5) Summarizing and reporting the results: The summary of the findings, representing the last stage of the five-stage framework for conducting a scoping review, is reported in the following section.

Results and Discussion

The current review allowed us to take a bird's eye view of the different methodologies used to circumvent many challenges associated with the integration of task-based fMRI to guide dMRI tractography. We will address the key findings one by one, and break down the advantages and inconveniences associated with the different approaches that were used in the reviewed articles. Note that there are more findings than research questions because more than one finding can correspond to the same research question. These findings might be helpful to readers interested in integrating task-based fMRI to guide dMRI tractography. Let us remember that even if some methods were more predominant compared to others, it is not necessarily a pledge of their quality.

Database search and trends through the years

Finding 1: The overlay approach is the most commonly used when compared with fusion and integration for the combination of fMRI with dMRI. [Research question #1]

A total of 504 (61%) primary experiments had acquired more than one brain imaging modality, and 439 (53%) had acquired fMRI along with dMRI data. Among the 439 studies that had acquired fMRI along with dMRI data, 267 (58%) used an overlay approach, 55 (12%) used a data fusion approach, and 136 (30%) used an integration approach (Figure 3B). Only 80 studies (10%) had integrated task-based fMRI results to guide tractography. Conturo et al., 1999 were the first to adopt this integrative framework. All the included articles are reported in Table 1.

Table 1: 80 studies included references with the data charted to produce most of the figures and statistics we reference throughout the scoping review

Studies		Sample description				dMRI and tractography parameters					Multimodal integration parameters		
Fig. 4	Fig.5B	Table. 2			Fig. 5A	Table. 3		Fig. 7A	Fig. 7B	Fig 7C	Fig. 9A	Fig. 9C	Fig. 9B
Articles	Topic	Total	Patients	Controls	Population	Gradient directions	model fitted	Tractography Algorithm	Seeding method	Tractography space	track selection	White and Grey matter interface method	Seed regions transferred from native to standard
Conturo et al. 1999	Vision	4	-	4	Healthy	12	DTI	Unknown	N/A	Native	Cluster	Displace ROIs	fMRI single-subject analysis
Guye et al. 2003	Motor	9	1	8	BT	54	DTI	Unknown	N/A	Native	Other	Displace ROIs	fMRI single-subject analysis
Kim et al. 2005	Vision	N/A	-	N/A	Healthy	N/A	DTI	Unknown	N/A	Native	Cluster	Others	fMRI single-subject analysis
Powell et al. 2006	Language	10	-	10	Healthy	54	DTI	Probabilistic	Seed	Native	Trace VOIs	Others	Reverse normalization
Schonberg et al. 2006	Motor	14	9	5	BT	6	DTI	Unknown	N/A	Native	Sphere	Displace ROIs	fMRI single-subject analysis
Cherubini et al. 2007	Motor	9	2	7	TBI	12	DTI	Probabilistic	Seed	Native	Cluster	N/A	Reverse normalization
Powell et al. 2007	Language	24	14	10	TLE	54	DTI	Probabilistic	Seed	Native	Trace VOIs	Others	Reverse normalization
Takahashi et al. 2007	Memory	20	-	20	Healthy	15	DTI	Probabilistic	Seed	Native	Cluster	N/A	Reverse normalization
Upadhyay et al. 2007	Audition	8	-	8	Healthy	15	DTI	Probabilistic	Seed	Native	Cluster	Dilate ROIs	fMRI single-subject analysis
Saur et al. 2008	Language	33	-	33	Healthy	61	DTI	Probabilistic	Seed	Native	Sphere	Rim of gray matter	Reverse normalization
Staempfli et al. 2008	Motor	6	-	6	Healthy	15	DTI	Unknown	N/A	Native	Sphere	Others	fMRI single-subject analysis
Bonzano et al. 2009	Memory	41	23	18	MS	15	DTI	Probabilistic	Seed	Native	Cluster	Dilate ROIs	Reverse normalization
Lanyon et al. 2009	Vision	10	-	10	Healthy	32	DTI	Deterministic	Whole-brain	Native	Trace VOIs	N/A	fMRI single-subject analysis
Morgan et al. 2009	Language	12	-	12	Healthy	32	DTI	Deterministic	Seed	Native	Cluster	Others	Reverse normalization

Uzuki et al. 2009	Motor	19	19		BT	42	DTI	Unknown	N/A	Native	N/A	N/A	fMRI single-subject analysis
Yang et al. 2009	Motor	11	-	11	Healthy	32	DTI	Probabilistic	Seed	Native	Cluster	N/A	fMRI single-subject analysis
Kleiser et al. 2010	Motor	11	8	3	BT	15	DTI	Probabilistic	Seed	Native	Sphere	Others	fMRI single-subject analysis
Mazerolle et al. 2010	Motor	10	-	10	Healthy	30	DTI	Deterministic	Whole-brain	Native	Cluster	Dilate ROIs	fMRI single-subject analysis
Moisset et al. 2010	Pain	11	-	11	Healthy	25	DTI	Unknown	N/A	Native	N/A	N/A	N/A

Table 1: (continued)

Studies		Sample description				dMRI and tractography parameters					Multimodal integration parameters		
Fig. 4	Fig.5B	Table. 2			Fig. 5A	Table. 3		Fig. 7A	Fig. 7B	Fig 7C	Fig. 9A	Fig. 9C	Fig. 9B
Articles	Topic	Total	Patients	Controls	Population	Gradient directions	model fitted	Tractography Algorithm	Seeding method	Tractography space	track selection	White and Grey matter interface method	Seed regions transferred from native to standard
Saur et al. 2010	Language	33	-	33	Healthy	61	DTI	Probabilistic	Seed	Native	Sphere	Rim of gray matter	Reverse normalization
Umarova et al. 2010	Attention	26	-	26	Healthy	61	DTI	Probabilistic	Seed	Native	Sphere	Rim of gray matter	Reverse normalization
Blank et al. 2011	Audition	19	-	19	Healthy	60	DTI	Probabilistic	Seed	Native	Sphere	Displace ROIs	fMRI single-subject analysis
Brauer et al. 2011	Language	20	-	20	Healthy	60	DTI	Unknown	N/A	Standard	Other	N/A	Averaged “DT image”
Ethofer et al. 2011	Vision	22	-	22	Healthy	30	DTI	Probabilistic	N/A	Native	Cluster	N/A	Reverse normalization
Hong et al. 2011	Motor	19	-	19	Healthy	32	DTI	Probabilistic	Seed	Native	Cluster	N/A	fMRI single-subject analysis
Schott et al. 2011	Memory	28	-	28	Healthy	N/A	DTI	Probabilistic	Seed	Native	Sphere	N/A	Reverse normalization
Wahl et al. 2011	Motor	28	16	12	MS	12	DTI	Unknown	Seed	Native	Cube	Others	fMRI single-subject analysis

Anderson et al. 2012	Motor	10	-	10	Healthy	64	DTI	Unknown	N/A	Native	Cluster	Others	fMRI single-subject analysis
Broser et al. 2012	Language	15	-	15	Healthy	60	HARDI	Probabilistic	Seed	Native	Other	N/A	fMRI single-subject analysis
Ethofer et al. 2012	Audition	22	-	22	Healthy	30	DTI	Probabilistic	N/A	Native	Cluster	Others	N/A
Greenberg et al. 2012	Attention	5	-	5	Healthy	257	DSI	Deterministic	Seed	Native	Cluster	Displace ROIs	fMRI single-subject analysis
Gschwind et al. 2012	Vision	24	-	24	Healthy	30	DTI	Probabilistic	Seed	Native	Sphere	Displace ROIs	Reverse normalization
Iidaka et al. 2012	Vision	30	-	30	Healthy	64	DTI	Probabilistic	Seed	Native	Cluster	N/A	N/A
Lee et al. 2012	Motor	10	-	10	Healthy	32	DTI	Probabilistic	Seed	Native	Trace VOIs	N/A	fMRI single-subject analysis
Shimono et al. 2012	Vision	11	-	11	Healthy	16	DTI	Probabilistic	Seed	Native	N/A	N/A	fMRI single-subject analysis
Vry et al. 2012	Motor	23	-	23	Healthy	61	DTI	Probabilistic	Seed	Native	Sphere	Rim of gray matter	Reverse normalization
Bonner et al. 2013	Language	22	-	22	Healthy	30	DTI	Deterministic	N/A	Standard	Cluster	Dilate ROIs	Averaged “DT image”
Bray et al. 2013	Vision	32	-	32	Healthy	60	HARDI	Probabilistic	Seed	Native	Cluster	N/A	fMRI single-subject analysis

Table 1: (continued)

Studies		**Sample description**				**dMRI and tractography parameters**					**Multimodal integration parameters**		
Fig. 4	**Fig.5B**	**Table. 2**			**Fig. 5A**	**Table. 3**		**Fig. 7A**	**Fig. 7B**	**Fig 7C**	**Fig. 9A**	**Fig. 9C**	**Fig. 9B**
Articles	**Topic**	**Total**	**Patients**	**Controls**	**Population**	**Gradient directions**	**model fitted**	**Tractography Algorithm**	**Seeding method**	**Tractography space**	**track selection**	**White and Grey matter interface method**	**Seed regions transferred from native to standard**
Caeyenberghs et al. 2013	Executive Function	31	16	17	TBI	64	DTI	Deterministic	Whole-brain	Native	Sphere	N/A	N/A
Ethofer et al. 2013	Vision	29	-	29	Healthy	30	DTI	Probabilistic	N/A	Native	Cluster	N/A	fMRI single-subject analysis

Griffiths et al. 2013	Language	30	16	14	PSA	64	DTI	Probabilistic	Seed	Native	Cluster	N/A	Reverse normalization
Hartwigsen et al. 2013	Language	17	-	17	Healthy	60	DTI	Probabilistic	Seed	N/A	Sphere	N/A	N/A
Klein et al. 2013	Arithmetic	33	-	33	Healthy	61	DTI	Probabilistic	Seed	Native	Sphere	Rim of gray matter	Reverse normalization
Lee et al. 2013	Motor	14	-	14	Healthy	32	DTI	Deterministic	N/A	Native	N/A	N/A	fMRI single-subject analysis
Lemaire et al. 2013	Language	12	-	12	Healthy	31	DTI	Unknown	N/A	Native	Cube	Displace ROIs	fMRI single-subject analysis
Oguri et al. 2013	Motor	25	-	25	Healthy	81	DTI	Probabilistic	Seed	Native	Cluster	N/A	fMRI single-subject analysis
Pyles et al. 2013	Vision	5	-	5	Healthy	362	DSI	Deterministic	N/A	Native	Cluster	Dilate ROIs	fMRI single-subject analysis
Szczepanski et al. 2013	Attention	14	-	14	Healthy	60	DTI	Probabilistic	Seed	Native	Other	N/A	fMRI single-subject analysis
Gao et al. 2014	Memory	38	13	25	AD	15	DTI	Unknown	N/A	Native	Cluster	N/A	Reverse normalization
Iwabuchi et al. 2014	Language	21	-	21	Healthy	30	DTI	Probabilistic	Seed	N/A	Cluster	Displace ROIs	N/A
Javad et al. 2014	Audition	14	-	14	Healthy	64	HARDI	Probabilistic	Seed	Native	Sphere	N/A	Reverse normalization
Jeon et al. 2014	Executive Function	19	-	19	Healthy	60	DTI	Probabilistic	Seed	Native	Sphere	Displace ROIs	Reverse normalization
Lee et al. 2014	Motor	10	-	10	Healthy	32	DTI	Probabilistic	Seed	Native	Cluster	N/A	fMRI single-subject analysis
Preti et al. 2014	Language	68	29	39	AD	12	DTI	Deterministic	Whole-brain	Native	Cluster	Dilate ROIs	Normalized tractogram

Table 1: (continued)

Studies		Sample description		dMRI and tractography parameters				Multimodal integration parameters		
Fig. 4	Fig.5B	Table. 2	Fig. 5A	Table. 3	Fig. 7A	Fig. 7B	Fig 7C	Fig. 9A	Fig. 9C	Fig. 9B

Articles	Topic	Total	Patients	Controls	Population	Gradient directions	model fitted	Tractography Algorithm	Seeding method	Tractography space	track selection	White and Grey matter interface method	Seed regions transferred from native to standard
Thomalla et al. 2014	Executive Function	30	15	15	GTS	24	DTI	Probabilistic	Seed	Native	Sphere	N/A	Reverse normalization
Whittingstall et al. 2014	Vision	18	-	18	Healthy	60	HARDI	Probabilistic	Seed	Native	Cluster	Rim of gray matter	fMRI single-subject analysis
Wu et al. 2014	Language	36	18	18	SCZ	362	DSI	Deterministic	Seed	Native	Sphere	Dilate ROIs	N/A
Gomez et al. 2015	Vision	26	8	18	DP	30	HARDI	Probabilistic	Seed	Native	Sphere	Others	fMRI single-subject analysis
Hakun et al. 2015	Executive Function	18	-	18	Healthy	36	DTI	Probabilistic	Seed	Native	Cluster	N/A	Reverse normalization
Jouen et al. 2015	Language	19	-	19	Healthy	60	DTI	Deterministic	Whole-brain	Native	Sphere	N/A	Reverse normalization
Leroux et al. 2015	Language	34	17	17	SCZ	21	DTI	Probabilistic	Seed	Native	Cluster	N/A	N/A
Musso et al. 2015	Audition	11	-	11	Healthy	61	DTI	Probabilistic	Seed	Native	Sphere	Rim of gray matter	Reverse normalization
Péron et al. 2015	Audition	15	-	15	Healthy	30	DTI	Probabilistic	Seed	Native	Sphere	N/A	Reverse normalization
Riley et al. 2015	Vision	43	24	19	TLE	64	DTI	Probabilistic	Seed	Native	Sphere	Displace ROIs	Reverse normalization
Vry et al. 2015	Motor	24	-	24	Healthy	61	DTI	Probabilistic	Seed	Native	Sphere	Rim of gray matter	Reverse normalization
Feng et al. 2016	Language	26	-	26	Healthy	30	DTI	Probabilistic	Seed	Native	Sphere	N/A	N/A
Hamzei et al. 2016	Motor	116	-	116	Healthy	61	DTI	Probabilistic	N/A	N/A	Sphere	Rim of gray matter	N/A
Niu et al. 2016	Motor	16	16		BT	30	DTI	Probabilist	Seed	Native	Sphere	N/A	fMRI single-subject

								ic					analysis
O'Hanlon et al. 2016	Memory	48	22	26	22q11	61	HARDI	Deterministic	Whole-brain	Native	Cluster	N/A	Reverse normalization
Reid et al. 2016	Motor	37	37	-	CP	64	HARDI	Probabilistic	Seed	Native	Cluster	Displace ROIs	fMRI single-subject analysis

Table 1: (continued)

Studies		Sample description				dMRI and tractography parameters					Multimodal integration parameters		
Fig. 4	Fig.5B	Table. 2			Fig. 5A	Table. 3		Fig. 6A	Fig. 6B	Fig 6C	Fig. 9A	Fig. 9C	Fig. 9B
Articles	Topic	Total	Patients	Controls	Population	Gradient directions	model fitted	Tractography Algorithm	Seeding method	Tractography space	track selection	White and Grey matter interface method	Seed regions transferred from native to standard
Scaccianoce et al. 2016	Language	22	1	21	PSA	12	DTI	Deterministic	Whole-brain	Standard	Sphere	Others	Done in standard space
Oechslin et al. 2017	Audition	59	-	59	Healthy	63	DTI	Probabilistic	Seed	Native	Sphere	Others	Reverse normalization
Reid et al. 2017	Motor	22	-	22	Healthy	64	HARDI	Probabilistic	Seed	Native	Cluster	Displace ROIs	fMRI single-subject analysis
Xing et al. 2018	Language	70	45	25	PSA	60	DTI	Probabilistic	Seed	Native	Sphere	N/A	Reverse normalization
Zhu et al. 2018	Motor	6	-	6	OBPP	30	DTI	Deterministic	Whole-brain	Native	Cluster	N/A	fMRI single-subject analysis
Sitek et al. 2019	Audition	10	10	-	Healthy	198	HARDI	Deterministic	Seed	Native	Cluster	N/A	Reverse normalization
Hazza et al 2019	Motor	19	10	9	BT	25	DTI	Probabilistic	Seed	Native	Cluster	N/A	fMRI single-subject analysis
Sanvito et al. 2020	Language	32	16	16	BT	60	HARDI	Probabilistic	Whole-brain	Native	Cluster	Dilate ROIs	fMRI single-subject analysis
Meissner et al. 2021	Vision	31	31	-	Healthy	33	DTI	Probabilistic	Seed	Native	Cluster	N/A	fMRI single-subject analysis
Gurtubay-Antolin et al. 2021	Vision and	16	16	-	Healthy	60	HARDI	Probabilistic	Seed	Standard	Sphere	Displace ROIs	Reverse normalization

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List of abbreviations used in table 1:

Model fitted:DSI → Diffusion Spectrum Imaging

- DTI → Diffusion Tensor Imaging
- HARDI → High Angular Resolution Diffusion Imaging

Population:

- 22q11 → 22q11 deletion syndrome
- AD → Alzheimer Disease
- BT → Brain Tumor
- DP → Developmental Prosopagnosia
- GTS → Gilles de la Tourette's Syndrome
- MS → Multiple Sclerosis
- OBPP → obstetric brachial plexus palsy
- PSA → Post-Stroke Aphasia
- SCZ → Schizophrenia
- TLE → Temporal Lobe Epilepsy
- TBI → Traumatic Brain Injury

The populations investigated - sample sizes and diagnoses

Finding 2: The average sample size was ≈17 and no guidelines currently exist with respect to sample size for fiber tracking, while some recommendations exist for fMRI. [Research question #2]

Study designs were heterogeneous, in so far that some investigated healthy individuals or patients, whereas others performed group comparisons (young healthy individuals, healthy elderly individuals, training groups, or patients). Therefore, the mean sample size for studies investigating healthy individuals was 18.6. Note that one study did not report their sample size, also the Hamzei et al., 2016 study was considered an outlier and removed from the analysis because it artificially inflated the descriptive statistics because it had 116 participants. The mean sample size for studies comparing groups was 16.0 for the patient group and 16.1 for the control group (see Table 2 for more information). To our knowledge, no current guidelines exist with respect to sample size for fiber tracking. However if the objective is to perform fiber tracking based on fMRI result, then the reader must be aware that small sample size offers unreliable results (Turner et al., 2018). Therefore, driving permanent conclusion about the brain organization from a small sample appears to be a risky bet. Figure 4 clearly demonstrate that most of the studies included in this scoping review were underpowered with respect to methodological studies about task-based fMRI (Thirion et al., 2007; Turner et al., 2018).

Table 2: Sample size descriptive statistics of included studies

	Mean	Mdn	SD	Min	Max
Healthy individuals (N=53)	18,6	18,0	9,8	4,0	59,0
Patient (N=26)	16,0	16,0	10,2	1,0	45,0
Control (N=22)	16,1	16,5	8,1	3,0	39,0

Finding 3: The integration of fMRI to guide fiber tracking can be performed with a clinical population, but it is not without shortcomings [Research question #3].

Most studies included in this scoping review investigated healthy individual (67.5%) while a minority investigated patients (32,5%). Figure 5 shows the partitioning of diagnoses across included studies and the partitioning of the neuroscientific domains investigated. Studies investigating clinical populations were focused on finding biomarkers (68%) or guiding possible intervention (32%). The most frequent problem reported was brain tumors with 7 published articles in the domain of neurosurgery (Guye et al., 2003; Kleiser et al., 2010; Niu et al., 2016; Schonberg et al., 2006; Uzuki et al., 2009). Even if the studies reviewed provided examples of successful application of this integration framework in patients, we remind the reader that they are not without shortcomings. Multimodal acquisition implies a longer time spent in the MRI scanner and this is not well suited to all clinical populations. As it was illustrated by Reid et al., 2016, acquiring good quality fMRI and dMRI data with patients can be a challenge due to excessive movement or non-compliance. Since the amount of clinical studies is relatively small with very heterogeneous studies it is difficult to draw clear conclusion of the applicability of this approach to find valid biomarkers in clinical population or to guide possible intervention. A detailed review of the designs and methods of studies that investigated clinical populations is available in the supplementary material.

Finding 4: No studies investigated the impact of using sets of fMRI and dMRI data obtained from different/independent samples. [a posteriori question]

Four of the reviewed studies used fMRI data obtained from samples different to, or independent of, those from the dMRI data obtained to perform their functionally driven fiber tracking (Gurtubay-Antolin et al., 2021; Hartwigsen et al., 2013; Klein et al., 2013; Musso et al., 2015). According to Klein et al., 2013 and Musso et al., 2015, using independent samples across MRI modalities strengthens the results because it reduces the chances that unknown anatomical peculiarities of a sample influence the overall results. However, Umarova et al., 2010 adopted the opposite point of view on this topic stating that "the use of regions of interest, obtained in other studies, may lead to a systematic error also due to the different spatial preprocessing." To our knowledge, no studies have investigated the impact of using sets of fMRI and dMRI data obtained from different/independent samples. This kind of investigation should be carried out in the near future by experienced fiber-tracking methodologists. In the meantime, if researchers endeavor to review the fMRI meta-analysis literature and drive fiber-tracking from the significant MNI coordinates in their dMRI data sample (or open source dMRI data sample), then they should be aware that this procedure could have an unprecedented impact on their results.

Diffusion MRI and tractography parameters

Finding 5: Higher order microstructure modeling strategies are under-used when integrating task-based fMRI to guide fiber-tracking. [Research question #4].

In Table 3 we report the descriptive statistics of the dMRI acquisition parameters by the microstructure modeling categories (DTI, high angular resolution diffusion imaging [HARDI], and diffusion spectrum imaging [DSI]) used in the 80 selected studies. Most studies included (66/80 = 82.5%) opted for a tensor model (DTI), and 11 of these studies used a two principal direction tensor model. Out of the 11 studies using HARDI, 10 (90%) opted for the fiber orientation distribution (FOD) from the constrained spherical deconvolution approach, and another used a ball and stick model. The ones who used DSI computed the orientation distribution function (ODF) from Q-ball imaging.

Table 3: dMRI acquisition parameters descriptive statistics by the microstructure model

	b value s/mm2					# directions				
Microstructure model	**Mode**	**Mean**	**SD**	**Min**	**Max**	**Mode**	**Mean**	**SD**	**Min**	**Max**
DSI = (N=3)	7000 (N=2)	6000	1732	4000	7000	362	327	61	257	362
DTI (N=66)	1000 (N=46)	1037	719	600	3000	30	38,88	20	3	81
HARDI (N=11)	3000 (N=3) 1000 (N=3)	1755	861	900	3000	60	71	43	30	198

Even if higher order microstructure modeling strategies have been validated for some time (e.g., Q-ball imaging since 2004), our data clearly suggest that the tensor model (DTI) is still the leading model when integrating fMRI to guide fiber-tracking, and it does not seem that researchers adopted higher order models as time progressed (see Figure 6). This can be considered as "bad news", considering that DTI fails to track properly in brain regions where white matter configuration is more complex (e.g., crossing fibers). Studies have shown that complex white matter configurations represent approximately 90% of white matter voxels (Descoteaux, 2008; Jeurissen et al., 2013). Furthermore, there is no reason to justify the use of DTI for fiber-tracking in reviewed articles that had acquired 45 or more independent diffusion weighted encoding direction with b-values between 1000-3000 s/mm^2 because

these parameters are relatively well suited to many HARDI models (Descoteaux & Poupon, 2012; Tournier, Calamante, & Connelly, 2013). The fact that researchers continue to use DTI for fiber tracking is not isolated to the domain of the integration of fMRI to tractography. This has been declared the first of the "Seven Deadly Sins" of fiber tacking (Calamante, 2019; Farquharson et al., 2013; Jones, 2010b). We remind the reader that DTI is still a valuable tool to estimate microstructural properties such as fractional anisotropy (FA) and other metrics. Nevertheless, DTI is not well suited for fiber tracking, while higher order microstructure models are proven to be more robust for this task (Calamante, 2019; Farquharson et al., 2013). Moving beyond the tensor model requires the consequent adaption of dMRI data acquisition protocols to ensure optimal HARDI parameter estimation. The reader can find such information in the following references: Descoteaux & Poupon, 2012 and Tournier et al., 2013.

Tractography specifications

Finding 6: Publications fail to report the bare minimal information about tractography parameters [a posteriori question]

We would like to emphasize that 39% of the reviewed studies did not clearly specify the number of streamlines generated per seed regions, 23% did not clearly specify if they performed whole-brain or seed region based tractography, 15% did not specify the nature of the fiber-tracking algorithm that was used, and 4% did not clearly specify if fiber tracking was performed in a native or standard space. This is problematic because it does not allow full appreciation of the extent of the results, precludes replicability of the findings, and introduces inconsistencies for future systematic review or meta-analysis. Descriptive statistics and further information about the number of streamlines generated per seed regions are depicted in supplementary Table 1.

Finding 7: Probabilistic algorithms are preferred to deterministic algorithms as they offer important advantages [Research question #6].

In the 80 articles selected, 66% performed probabilistic fiber tracking, while 19% used a deterministic algorithm (Figure 7A). The use of probabilistic tractography algorithms has increased over time, when task-based fMRI results have been integrated to guide tractography (see supplementary Figure 2). This is not surprising, considering the advantages over deterministic tractography. Deterministic tractography algorithms are sensitive to a single principal direction, and tracking results can be easily corrupted/penalized by regions with higher curvature, complex organization, or noisy data (Alexander, 2010; Descoteaux and Poupon, 2012; Parker, 2010). In contrast, probabilistic fiber tracking offers the advantage of considering all the possible directions (as opposed to only the principal direction), and provides a quantitative indicator of the confidence in the tracking results, which is not negligible (Descoteaux and Poupon, 2012; Parker, 2010).

Track selection methods

Finding 8: Seed based tractography is preferred over filtering whole-brain fiber tracking [Research question #6].

Most of the selected articles (65%) ran a seed region based tractography, while 11% performed whole-brain fiber tracking and then filtered out their track of interest using functionally derived regions of

interest (Figure 7B). To our knowledge, the advantages of seed to seed tractography over filtering whole-brain tractography (or the other way around) remain to be studied more extensively before deriving a conclusion on this topic. However, some evidence suggests that seed based tractography yields more chances for succeeding in delineating fiber bundles that are harder to track, when compared to whole-brain fiber tracking (Chamberland et al., 2014).

The following articles performed single seed fiber tracking, which means that they ran fiber tracking from an activated ROI toward all other points in the brain: (Bonzano et al., 2009; Cherubini et al., 2007; Guye et al., 2003; Kleiser et al., 2010; Little and Holloway, 2007; Powell et al., 2007, 2006; Thomalla et al., 2014). The single seed tracking method allows the generation of a structural connectivity map (or structural connectivity profile) of the seed regions with the rest of the brain. Powell et al., 2007 argues that single seed region fiber tracking "allows a global assessment of the pattern of connectivity without imposing strong prior user knowledge" and adds that "two-region approaches also have the disadvantage of potential bias due to the a priori assumption that connections between the two sites do actually exist". This argument highlights an advantage of this method, however, one must keep in mind that single seed region fiber tracking is a non-commutative process (tracking from a starting point does not necessarily guarantee the same result when tracking is initiated from the end points initially obtained) (Caan, 2016; Jones, 2010b). Furthermore, it is often well-justified to track back and forth between a seed ROI and a target ROI to put a hypothesis to the test or verify the presence of a disconnection in patients between two normally connected regions. Even if some "fixed or standardized" set of tractography parameters have been suggested in the literature, we remind the reader that fiber tracking in a clinical population could be influenced by those parameters because of the patient's peculiarities, as illustrated in Chamberland et al., 2014.

Finding 9: Fiber tracking is performed in the participant's dMRI native space when integrating task-based fMRI to guide fiber tracking, as suggested by the best practices [Research question #6].
The majority (90%) of assessed articles performed fiber tracking in the participants' dMRI native space (Figure 7C). This is considered "best practice" because performing fiber tracking in native unwrapped images prevents misregistration errors and failure of b-matrix rotation (Gao et al., 2014; Jones and Cercignani, 2010). In a different manner, 5 articles (6%) performed fiber tracking in a standard space (Figure 7C). Scaccianoce et al., 2016 warped their participants' DTI data in MNI space before performing fiber tracking, while Bonner, Peelle, Cook, & Grossman, 2013 and Brauer, Anwander, & Friederici, 2011 produced a single averaged "DT image" across the participants, then warped this "DT image" in a standardized space for fiber tracking.

Finding 10: False negatives could be prevented by adopting a track profiling approach when measuring white matter microstructural properties over a track. [Research question #12].
Out of the 80 articles selected, 29 (36%) analyzed white matter microstructural properties such as FA and other metrics (AD, RD, MD, and others). Most of these articles (27/29 = 93%) calculated a mean value over the whole track. This procedure is relatively common; however, it could potentially lead to type II errors (false negatives) stating that no significant variation of the metric is observed on the track. As it was demonstrated by Gomez et al., 2015, subtle and meaningful variation can be detected

in subsections of a track, while it is not detected when using the average of the whole track. This makes sense, knowing that tracks are formed of multiple individual streamlines each having different gross trajectories, length, shape, and branching (Chamberland et al., 2019). For this reason, we believe that adopting a track profiling approach when performing tractometry could be beneficial. This means collecting multiple samples of microstructural properties across/along the track (subsections), instead of only averaging over the course of the whole track (Chamberland et al., 2019; Cousineau et al., 2016). Only two articles calculated the white matter microstructural properties on subsections of the tracks (see Gomez et al., 2015 and Reid, Sale, Cunnington, Mattingley, & Rose, 2017 for more details).

Finding 11: Sub-optimal fiber tracking strategies adopted by the scoped articles could promote false positives [Research question #6].

Only one of the reviewed articles (Gurtubay-Antolin et al., 2021) performed their fiber tracking using well-developed tracking strategies such as Anatomically Constrained Tractography (ACT) (Smith et al., 2012a), Continuous Map Criterion (CMC) (Lemkaddem et al., 2014), or Particle Filtering Tractography (PFT) (Girard et al., 2014). These tools integrate anatomical priors derived from T1-weighted image tissue segmentation, which offers higher spatial resolution than dMRI images, into the tracking process to make the tracking results more consistent with knowledge obtained from other studies that use invasive means. In the case of ACT, these anatomical priors are used to preclude fiber tracking in non-white matter tissues (i.e., cerebrospinal fluid, cortical gray matter, sub-cortical gray matter, and skull). This latter procedure is less prone to false positives and biases due to partial volume effect and FA map thresholding strategies (i.e., tracking in regions where FA > 0.25) where FA values fall within white matter voxels containing a more complex organization (Jeurissen et al., 2013; Jones and Cercignani, 2010). It also refines fiber tracking by using a set of rules regarding plausible termination points (gray matter) and non-plausible termination points (cerebrospinal fluid and white matter). These tools were developed in 2012 and 2014, so we understand why the reviewed articles published before this period did not use these strategies to refine their results. However, we highly recommend incorporating these strategies for future research that will integrate task-based fMRI results to guide tractography. Furthermore, we stress that Anatomically Constrained Tractography (ACT) can serve as a potential problem solver to the issue of the gray/white matter interface (see Finding 20), as it can flexibly perform tracking in ROIs if classified/defined properly in the ACT framework.

Finding 12: Lack of convergent and divergent validity diminish the overall specificity and confidence of the findings [Research question #11, 12 and 13].

Of the reviewed studies, 66/80 (82.5%) did not cross validate their finding through other sources such studies that uses more invasive means (e.g., animal tracer studies, Wallerian degeneration, myelogenic development and post-mortem human brain dissection). We argue that authors ought to consider this option, when possible, to support and strengthen their findings. On the other hand, we understand that is it not always possible to support tractography findings with converging evidence from other invasive means. A common issue is to try to compare/support findings about the human language system with animal studies. Such comparisons cannot be established in a straightforward manner due to the large evolutionary gap between human language and language in other species (Rilling et al., 2008).

When presenting their fiber tracking results, 54/80 (67.5%) of the selected articles labeled the tracts according to a known white matter structure (from a DTI, tractography, or white matter atlas), while the other 26/80 (32.5%) did not. It can be difficult for readers to understand the practical or theoretical implications of a statement such as "there were structural connections between the left inferior frontal gyrus and the left angular gyrus". The statement provides no information about the anatomical underpinning of the so-called structural connection. Therefore, we argue that tractography results could become more meaningful if they were properly labeled according to a known white matter structure (e.g., "there were structural connections between the left inferior frontal gyrus and the left angular gyrus, passing by the superior longitudinal fasciculus [SLF-II]"). Labeling tractography results also allows the evaluation of the consistency of tractography findings across studies. Furthermore, it offers the opportunity to verify if the tractography results are part of a known white matter structure or are segregated from it. In their studies, Gomez et al., 2015 provide rich information about the topographic organization of the face and place selective functionally defined white matter tracts in relation to the inferior longitudinal fasciculus (ILF).

Another issue related to studies that performed measures of white matter microstructural properties is the lack of control/comparison tracts. A minority of studies (18/80 or 22.5%) included a control track, or a form of control tract, for quality assurance or comparison purposes, while others did not. Few articles reported significant microstructural property differences between groups in the investigated track, without providing measurements from a control/comparison tract. This is problematic because it is impossible to know if the difference is specific to this track, or is a more general characteristic of the population investigated (i.e., the difference is present in all the white matter). Control/comparison tracks can take multiple forms, such as the extracted values in a well know bundle, such as the corticospinal track (CST), or the simple delineation of the "same tract" in the opposite hemisphere. We argue that authors should provide control/comparison tracks when comparing white matter microstructural properties between groups to support the validity and specificity of their findings. Examples of articles providing different forms of control/comparison tracts are Bonner et al., 2013a; Ethofer et al., 2011; Gomez et al., 2015; Reid et al., 2017a, 2016; and Upadhyay et al., 2007a.

MRI analysis packages

Finding 13: FSL and SPM were the most frequently used software [Research question #5].

The software that was most frequently used to pre-process dMRI data and perform tractography was FSL (www.fmrib.ox.ac.uk/fsl) accounting for 43% and 37% of the articles, respectively. Other packages were used and are reported in Figures 8A and 8B. SPM (https://www.fil.ion.ucl.ac.uk/spm/software/) was the software that was used by most of the reviewed studies (74%) to perform fMRI data processing and analysis. Figure 8C reports the other software used for fMRI data analysis. Although DIPY (https://dipy.org/) is a toolbox frequently employed in tractography studies, surprisingly, only one of the studies included in the present scoping review report using this toolbox in their analysis.

Methods to derive tractography seed region from task-based fMRI

A critical aspect of this integrative approach is deriving seed or filter regions from task-based fMRI in order to guide the tractography. Various methods were used to do so across the selected articles. We

classified these methods into four main categories: the cluster method, the sphere method, the manual tracing method, and others (Figure 9A).

Finding 14: Clusters of activation and spherical regions of interest based on fMRI are often used to guide fiber tracking [Research question #7].

The most frequently performed seeding/filtering method was the cluster method, representing 36 (45%) of the selected articles. This is probably the most straightforward method, as it "only" saves the task-based fMRI activation clusters into an object that can be used for fiber tracking directly from the neuroimaging statistical package (i.e., a binary mask or n-ary mask). It also has the advantage of reflecting the whole extent of the activated brain region (relative to the threshold applied). This seeding/filtering method (or extremely similar ones) was used by the following authors: Anderson et al., 2012; Bonner et al., 2013a; Bonzano et al., 2009; Bray et al., 2013; Cherubini et al., 2007; Conturo et al., 1999; Ethofer et al., 2013, 2012, 2011; Gao et al., 2014; Greenberg et al., 2012; Griffiths et al., 2013; Hakun et al., 2015; Hazzaa et al., 2019; Hong and Jang, 2011; Iidaka et al., 2012; Iwabuchi and Kirk, 2014; Kim and Kim, 2005; Lee et al., 2014; Leroux et al., 2015; Mazerolle et al., 2010; Morgan et al., 2009; O'Hanlon et al., 2016; Oguri et al., 2013; Preti et al., 2014; Pyles et al., 2013; Reid et al., 2017b, 2016; Sanvito et al., 2020; Sitek et al., 2019; Takahashi et al., 2007; Upadhyay et al., 2007a; Whittingstall et al., 2014; Xi et al., 2018; Yang et al., 2009. However, it is not always feasible or realistic to directly use clusters as seeds/filtering regions, given their varying size and shape and wide brain surface coverage. Therefore, it becomes difficult to make sense of such clusters, and they might not be useful for fiber tracking.

The sphere method consists of placing a sphere ROI onto the coordinate of the peak activation point (or the center of gravity) of a cluster. This offers the advantage of ruling out the previously mentioned issue related to cluster size and shape. Sphere sizes varied across the 30 articles using this method. Sphere radius size varied across articles (see Table 1 for descriptive statistics) and we do not know exactly what the impacts of sphere radius size are on tractography results. The most frequent sphere size radius used was 4 mm and 5 mm in 15 out of 30 studies. It seems very improbable that the brain regions we are trying to identify with fMRI are reliably represented with large spheres (> 8 mm radius) that jump across multiple gyri/sulci or white matter voxels. Without studies and precise guidelines regarding the "ideal" radius of sphere ROIs it is difficult to recommend anything beyond stating that 4- and 5-mm radii were the most frequently used in the reviewed articles (see Table 1). Note that the user must remain vigilant about the risk of resampling errors when carrying ROIs between different MRI spatial resolutions (nearest neighbor interpolation should be used when reslicing images). The sphere method (or extremely similar methods) was performed in the following articles: Blank et al., 2011; Caeyenberghs et al., 2013; Feng et al., 2016; Gomez et al., 2015; Gschwind et al., 2012; Gurtubay-Antolin et al., 2021; Guye et al., 2003; Hamzei et al., 2016; Hartwigsen et al., 2013; Javad et al., 2014; Jeon et al., 2014; Jouen et al., 2015; Klein et al., 2013; Kleiser et al., 2010; Musso et al., 2015; Niu et al., 2016; Oechslin et al., 2017; Péron et al., 2015; Riley et al., 2015; Saur et al., 2010, 2008; Scaccianoce et al., 2016; Schonberg et al., 2006; Schott et al., 2011; Shimono et al., 2012; Staempfli et al., 2008; Vry et al., 2015, 2012; Wu et al., 2014; Xing et al., 2018.

The manual tracing method implies to manually draws the cluster of activation to transform it into a ROI (or volume of interest [VOI]) to seed/filter fiber tracking. It was used in the following four

articles: Lanyon et al., 2009; Lee et al., 2012; and Powell et al., 2007, 2006. Note that this technique is highly similar to the cluster method previously mentioned. However, the manual drawing method is user dependent, which may lead to human errors, and is far more time consuming than the cluster method.

The category "others" encompasses different seeding/filtering methods that were used by two or fewer articles, and is further described in the supplementary material. To our knowledge, the other methods used to derive ROIs from task-based fMRI do not offer any advantages over the above-mentioned methods. Finally, four of the selected studies did not clearly state how they derived their seed regions for fiber tracking, based on task-based fMRI activation results.

Table 4: Sphere size radius (in mm) descriptive statistics

Mode	Mdn	Mean	SD	Min	Max
4 (N=7)	5	5,5	2,21	2	11
5 (N=8)					

Methods used to match the multimodal MRI spaces

We previously mentioned that 90% of the selected studies performed tractography in the subject's native space (Figure 9C). This can be an issue, knowing that 44/80 (55%) of the selected studies performed a group-wise random effect fMRI analysis in a standard space (i.e., MNI template).

Finding 15: When performing group-wise fMRI analysis, most researchers used an inverse/reverse normalization procedure to return their ROIs in the participant's dMRI native space [Research question #8].

Few studies (10/80 = 12.5%) did not clearly specify how they managed to perform fiber tracking in the participant's dMRI native space when they ran group-wise analysis in a standardized template (Figure 9B). Most of these studies (30/44) solved this issue by returning their ROIs (i.e., fMRI cluster, sphere, or MNI coordinates) into the participant's dMRI native space by using a reverse/inverse normalization procedure (Bonzano et al., 2009; Cherubini et al., 2007; Ethofer et al., 2011; Gao et al., 2014; Griffiths et al., 2013; Gschwind et al., 2012; Gurtubay-Antolin et al., 2021; Hakun et al., 2015; Javad et al., 2014; Jeon et al., 2014; Jouen et al., 2015; Klein et al., 2013; Morgan et al., 2009; Musso et al., 2015; O'Hanlon et al., 2016; Oechslin et al., 2017; Péron et al., 2015; Powell et al., 2007, 2006; Riley et al., 2015; Saur et al., 2010, 2008; Schott et al., 2011; Sitek et al., 2019; Takahashi et al., 2007; Thomalla et al., 2014; Umarova et al., 2010; Vry et al., 2015, 2012; Xing et al., 2018). This procedure consists of using the reversed deformation field obtained/saved during the T1-weighted image tissue segmentation step, and requires co-registration of all the MRI modalities to the participant's dMRI space before segmenting and normalizing the MRI data. It is also possible to keep multimodal MRI data in distinct spaces and save the normalization deformation fields for each modality, in order to ensure correspondence in the future. However, the latter involves an accumulation of residual errors across the different deformation fields used.

Four studies performed their fMRI analysis and then integrated their fiber tracking results in a standard space. Preti et al., 2014 and Scaccianoce et al., 2016 normalized their participants' whole-brain tractogram in MNI space and then filtered out the track of interest using the group-wise activated brain

regions. Streamlines obtained in the participant's dMRI native space can be warped to a standard template (i.e., MNI template) using software such as Megatrack (Dell'Acqua et al., 2015) or DIPY direct streamlines Normalization (https://dipy.org/) (Avants et al., 2011; Greene et al., 2018).

Bonner et al., 2013 and Brauer et al., 2011 produced a single averaged "DT image" across the participants. This averaged "DT image" was then warped in a standardized space and whole-brain tractography was performed. They then filtered out the track of interest using the group-wise activated brain regions.

Finding 16: When performing single subject fMRI analysis, one "simply" needs to ensure proper registration between the different MRI modalities [Research question #8].

Another straightforward method applied in 36/80 (45%) of the selected studies was to perform fMRI single-subject analysis (fixed effect) for each subject in their respective MRI native space (Anderson et al., 2012; Blank et al., 2011; Bray et al., 2013; Broser et al., 2012; Conturo et al., 1999; Ethofer et al., 2013; Gomez et al., 2015; Greenberg et al., 2012; Guye et al., 2003; Hong and Jang, 2011; Kim and Kim, 2005; Kleiser et al., 2010; Lanyon et al., 2009; Lee et al., 2014, 2013, 2012; Lemaire et al., 2013; Mazerolle et al., 2010; Niu et al., 2016; Oguri et al., 2013; Pyles et al., 2013; Reid et al., 2017b, 2016; Schonberg et al., 2006; Shimono et al., 2012; Staempfli et al., 2008; Upadhyay et al., 2007a; Uzuki et al., 2009; Wahl et al., 2011; Whittingstall et al., 2014; Yang et al., 2009). Therefore, one "simply" needs to insure proper registration between the different MRI modalities. Single-subject analysis in fMRI ensures suitable localization of brain activations, while respecting the individual's neuroanatomy. On the other hand, group-wise fMRI analysis provides more sensibility and reliability as the sample size increases (Geuter et al., 2018).

Methods to address the gray/white matter interface

fMRI aims to localize brain activations in the cortex and in subcortical nuclei where neural activity occurs and generate a detectable BOLD signal. However, fiber tracking is generally performed in white matter areas; it is not performed in cortical gray matter, sub-cortical nuclei, and cerebrospinal fluid, especially in the case of anatomically constrained tractography (Smith, Tournier, Calamante, & Connelly, 2012). Thus, it is a good idea to ensure that the fiber tracking seed and target ROIs are in contact, at least partially, with white matter to guarantee that streamlines reach their target (Whittingstall et al., 2014). Publications in this scoping review proposed various approaches to deal with this gray and white matter interface issue. We organized the different methods according to their similarities into five main categories: displace ROIs, rim of gray matter, dilate ROIs, others, and unknown (Figure 9C). A large number of these articles (34/80) did not clearly specify how they ruled out this gray and white matter interface issue.

Finding 17: The problem of white and gray matter interface might not always need to be addressed, but when it does, solutions have been proposed [Research question #8].

One question that arose when we realized that a considerable amount (45%) of the reviewed articles did not clearly specify how they ruled out this gray and white matter interface issue was "maybe it is not always necessary to manipulate the ROIs or the white matter fiber tracking mask to obtain descent fiber tracking?" In fact, as addressed by Gomez et al., 2015; Kleiser et al., 2010; and Staempfli et al., 2008, it is possible that spherical ROIs (from 3 to 7 mm radius) could be sufficient to guarantee contact with

white matter. This makes sense, knowing that the human cortex thickness is roughly 2.5 mm and ranges between 1 mm and 4.5 mm from one folding to another (Fischl and Dale, 2000). When using fMRI clusters as tractography ROIs, it is possible that the smoothing kernel applied during fMRI preprocessing solves the white and gray matter interface issue, as stated by Powell et al., 2006, 2007: "Spatial smoothing of the fMRI scans leads to blurring of activations across neighboring voxels, leading to activations which include both gray and white matter. This provides a relatively unbiased choice of white matter voxels for tractography seeding, avoiding the necessity to manually define the white matter voxels expected to subserve a particular gray matter area."

In their study, Schonberg et al., 2006 manually placed their seed ROIs on the directionally encoded color FA maps next to the fMRI activations. Lemaire et al., 2013 manually placed a cubic seed ROI within a white matter fascicle determined by a neuroanatomist. Conturo et al., 1999 constructed a 1-cm band that laterally followed the activated cortex.

In a different manner, 13 studies displaced the localization of seed ROIs to get around the issue of the gray and white matter interface. Some researchers displaced the center of the ROIs to the closest point of the gray/white matter junction, based on FA maps (Blank et al., 2011; Gschwind et al., 2012; Jeon et al., 2014; Riley et al., 2015). This point of gray/white matter junction is frequently defined using an FA threshold such as FA > 0.25 (where values < 0.2 are often considered to belong to gray matter). In a similar manner, Guye et al., 2003 selected a set of three voxels in the white matter under the local maxima based on FA maps. Although these methods might appear to be unbiased when compared to simple visual inspection or manual ROIs displacement, they are still prone to errors due to FA thresholding. Indeed, it is not considered good practice since it has been demonstrated that FA values fall within white matter voxel-containing complex fiber organization (i.e., fiber crossing, kissing, high curvature, and fanning) (Jones, 2010b).

Another approach (9/80) used to overcome the gray and white matter interface problem was to add a rim of gray matter to the tractography mask, to ensure that fiber tracking reaches cortical ROIs (Hamzei et al., 2016; Klein et al., 2013; Musso et al., 2015; Saur et al., 2010, 2008; Umarova et al., 2010; Vry et al., 2015, 2012). These articles do not clearly state how this procedure was performed. We corresponded with some of the original authors of these studies and one of them answered: "we expanded the white matter mask by a millimeter". In the same vein, Whittingstall et al., 2014 dilated the white matter mask by 1 spherical millimeter to allow tractography to reach cortical regions and sub-cortical nuclei. However, this procedure dilates the whole mask, which might include undesirable areas such as the ventricles.

Instead of dilating the white matter mask, some authors dilated the fMRI driven ROIs to ensure proper overlap with white matter voxels (8/80). The size of the dilation kernel ranged from two to six isotropic millimeters across studies (Bonner et al., 2013b; Bonzano et al., 2009; Mazerolle et al., 2010; Preti et al., 2012; Pyles et al., 2013; Upadhyay et al., 2007b; Wu et al., 2014).

The category "others" encompasses heterogeneous methods to ensure contact between functionally driven seed/filter ROIs and white matter that were used by three or fewer articles. Further description is available in the supplementary material.

Four articles projected activated clusters onto a gray/white matter boundary mesh and then performed fiber tracking from the surfaces vertices into participants' native dMRI space (Greenberg et al., 2012; Iwabuchi and Kirk, 2014; Reid et al., 2017a, 2016). This raised the question whether we should continue to perform analysis at the voxel level or move towards surface analysis. Recently, dMRI methodological studies provided strong support for the use of cortical surface to improve the precision of tractography (surface-enhanced tractography) (Glasser et al., 2016; St-Onge et al., 2018). Research into the combining fMRI and dMRI could consider this approach to address the issue of the gray/white matter interface.

Methods to present integrated results

Finding 18: Methods to present the results of this integrative framework were extremely heterogeneous [Research question #10].

The presentation of the results was extremely heterogeneous across the studies we scoped, since they had different research questions and methods. Some of these measured the microstructural properties of the white matter tracks while others investigated the structural connectivity or the reliability of reconstructed bundles across a group. Therefore, we will present some methods that were commonly used across the scoped literature.

Witthingstall et al. 2014 presented an example of how fiber tracking data from multiple participants can be integrated in a group statistic while remaining in its original native space. In their study, they assessed connection reproducibility across participants by reporting the percentage of subjects that had streamlines structurally connecting two ROIs (Figure 10A) (Whittingstall et al., 2014). In a analogous way, other authors derived structural connectivity measurements from the participant's fiber bundles reconstructed in their native space (Figure 10B) (Bray et al., 2013; Broser et al., 2012; Greenberg et al., 2012; Oguri et al., 2013; Pyles et al., 2013; Szczepanski et al., 2013; Upadhyay et al., 2007a). In the latter studies, the structural connectivity measurements were mostly based on the number of tracts connecting sets of ROIs. We remind the reader that methods to quantify structural connectivity are to be used with caution because they are still the subject of vigorous scientific debate (Jones, 2010b).

The following articles collected microstructural white matter properties (i.e., FA and other values) from the participant's tracts in their native space: Bonzano et al., 2009; Broser et al., 2012; Gao et al., 2014; Gomez et al., 2015; Griffiths et al., 2013; Gschwind et al., 2012; Kleiser et al., 2010; Moisset et al., 2010; O'Hanlon et al., 2016; Powell et al., 2006, 2007; Reid et al., 2017b, 2016; Riley et al., 2015; Schonberg et al., 2006; Upadhyay et al., 2007a; Wahl et al., 2011; Wu et al., 2014; Xing et al., 2018; and Yang et al., 2009. This approach allows the comparison of groups, the determination of the effect of an intervention/training, or the following of the recuperation/evolution of a patient's brain over time. Some of these have established correlation between the microstructural white matter properties and behavioral/cognitive measures (see Figure 11 for examples) (Gao et al., 2014; Gomez et al., 2015; Powell et al., 2007, 2006; Reid et al., 2016; Wu et al., 2014; Xing et al., 2018).

In order to represent fiber bundles in a common space, Javad et al. 2014 normalized tracts extracted from fMRI derived ROIs in a standard space to obtain a group-wise fascicle representation, where voxel intensity is proportional to the number of subjects in which the tracks were identified (Figure 12A) (Javad et al., 2014). Ethofer et al. 2012 also displayed tractography results in a standardized space

in a similar fashion. The degree of fiber connection overlap is illustrated in Figure 3 of their publication (Ethofer et al., 2012). In order to visualize fiber tracking results in a standardized space, Jeon et al. 2014 normalized the thresholded (10%) visitation maps and slightly smoothed the group overlapping pathways with a 1 mm full width half maximum filter (FWHM) (see Figure 6 of their article) (Jeon et al., 2014). Finally, many authors mentioned in this scoping review used a technique that estimates the probability that a voxel is connected by a direct path to both seed regions. The estimation is first done at the individual level, and then combined in a normalized space for visualization (Figure 12B) (Hartwigsen et al., 2013; Klein et al., 2013; Musso et al., 2015; Saur et al., 2010, 2008; Umarova et al., 2010; Vry et al., 2015, 2012). This method produces estimate maps called "probability index on forming part of the bundle of interest" (PIBI), and is further described by Kreher et al., 2008.

fMRI and dMRI tractography limitations

Finding 19: Identification of a structural link between functionally activated brain regions does not necessarily imply a causal role [a posteriori question]

Even if tractography identifies a clear structural connection between activated brain regions during a given cognitive process, researchers should remain cautious of straightforward interpretations of relationships between a given white matter tract and specific cognitive function because degenerate structure-function mappings impede this reasoning (Park and Friston, 2013). It is still necessary to look for converging evidence between fMRI, dMRI, and the patients' notes to establish strong structure/network to function relationships. We remind the reader that one limitation of dMRI tractography is that it cannot distinguish between efferent and afferent fibers (Jones, 2010b). Although it might be possible to infer a certain direction of the fMRI signal by using effective connectivity approaches, it would still be impossible to highlight the existence of feedforward connections in the fiber bundles. Hartwigsen et al., 2013 used dynamic causal modeling (DCM) to show facilitatory connectivity from the pre-supplementary motor area (pre-SMA) to the left dorsal premotor cortex during pseudoword repetition. This facilitatory connectivity was possible through the direct anatomical connection between the two cortical regions, as demonstrated by fiber tracking (Hartwigsen et al., 2013).

Conclusion

Our scoping review represents the first attempt to systematically gather, analyze, and summarize the literature describing 80 studies that integrated task-based fMRI results to guide tractography over the last two decades. Other reviews published previous to this did not adopt a systematic approach and were not focused on the topic of the integration of task-based fMRI with tractography (see Rykhlevskaia, Gratton, & Fabiani, 2008; Sui et al., 2014; Zhu et al., 2014). This makes the present article the most comprehensive reference document regarding methodological issues related to the integration of task-based fMRI with tractography. We have provided an exhaustive overview of the tools that currently exists to help researchers willing to integrate fMRI to guide tractography. This scoping review can be used by the neuroscientific community to 1) better understand possible strengths and limitations of the methods used in this field, 2) help design studies using this integrative approach, and 3) motivate researchers to fill the gaps identified.

We demonstrated that the overlay approach is still the dominant approach when combining fMRI with tractography (finding 1). When integrating fMRI to guide fiber tracking, clinical studies are feasible, but one must remember that multimodal acquisition implies a longer time spent in the MRI scanner, and this is not always suited to clinical populations. Furthermore, populations investigated were heterogeneous and most clinical studies focused on finding biomarkers. Validation studies and standardization of this approach to find clinical biomarker remains to be done (finding 3). We also highlighted that no studies have investigated the impact of using sets of fMRI and dMRI data obtained from different/independent samples and that this issue needs to be addressed in a near future (finding 4).

At this stage, it is still difficult for us to provide clear guidelines on “what to do” and “what not to do” when integrating fMRI to guide fiber tracking due to the lack of consensus among the reviewed articles and the lack of studies that measure the impact of each method on the results. However, this scoping review point out that the articles that integrated fMRI to guide dMRI tractography often failed to apply the current best practices for each MRI modality individually (findings 2,5,6,10 and11). Therefore, we believe that fMRI and tractography outcomes could be greatly improved by incorporating the best practice tackled in the paragraph related to each finding.

When it comes to the “integration step”, we have addressed the issues related to the usage of task-based fMRI activation results to guide tractography and how to deal with different MRI spaces across modalities (native and/or standardized) (findings 14,15 and 16). Solutions were proposed to circumvent the issues of the gray and white matter interface, yet few of these solutions implies data transformation (i.e. dilate or displace ROIs) and we don’t know what the impacts of such manipulations are. Surface based analysis appears to be an interesting candidate to overcome this issue and a consensus about moving towards surface analysis seems to gradually emerge (Glasser et al., 2016; Reid et al., 2016; St-Onge et al., 2018) (finding 17).

Researchers who are planning to integrate fMRI activation results to guide tractography should consider that fiber tracking can lead to potential false positives that do not necessarily reflect real anatomically proven fiber bundles. With this in mind, it should be considered good practice to 1) label

the tracking results according to a known white matter structure, 2) cross validate findings with other sources such studies that use more invasive means, 3) assess the amount of overlap between reconstructed track and know fiber bundles obtained with whole brain fiber tracking while making sure its topographical organization is plausible (finding 12). In the same vein, we remind the reader that the identification of a structural link between functionally activated brain regions does not necessarily imply its causal role in the function assessed. It is still necessary to look for converging evidence in the literature to establish strong structure/network to function relationships (finding 19).

Finally, the choice of the most well-suited approach should always be guided by the specific research question of the study.

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Supplementary material:

Results and discussion

The populations investigated -diagnoses

The most frequent problematic reported was brain tumors with 7 published articles in the domain of neurosurgery (Guye et al., 2003; Hazzaa et al., 2019; Kleiser et al., 2010; Niu et al., 2016; Sanvito et al., 2020; Schonberg et al., 2006; Uzuki et al., 2009). Most of these studies (5/7) investigated the advantages of integrating task-based fMRI to guide the tractography to follow the course of the corticospinal tract (CST) that has been displaced/deviated by tumors. They succeeded in tracking the CST and showed that this approach could benefit surgery planning. Using fMRI seed regions from motor tasks (e.g. hand grip, finger tapping, ankle flexion, etc.) help to better track the CST than classical anatomical seed placement in the motor cortex because the mass effect could cause anatomical and function distortion of the cortex (Kleiser et al., 2010; Niu et al., 2016). This seeding method shows no advantages as compared to anatomical seeding when it comes to track white matter infiltrated by the tumor because the partial volume effect significantly blurs the dMRI signal (Schonberg et al., 2006).

The neurodevelopmental disorder category contains three studies, but the clinical problematic are heterogeneous. **Cerebral palsy:** Reid, Cunnington, Boyd, & Rose, 2016 studied cerebral palsy patients to validate that their surface based fMRI-driven diffusion tractography method was suitable for clinical population that presents important anatomical distortion. They also demonstrate that their approach generates better results than standard voxel-based methods. They delineate the hand representation of the CST by using seed region provided by a hand flexion fMRI task. The authors highlight the fact that acquiring good quality fMRI and dMRI data with patients can be problematic. In their cases, they had to exclude six participants because of poor data quality, excessive movement or non-compliance with the fMRI task (Reid et al., 2016). **Developmental prosopagnosia:** In their study, Gomez et al., 2015 demonstrate that face and place selective brain regions (localized via fMRI and used as seed region for fiber tracking) in the ventral temporal cortex project tracts that are segregated one from another. They also provide clear indication that these functionally define white matter tracts are arranged in a parallel fashion in relation to the inferior longitudinal fasciculus (ILF). To do so they measured the distance from the center of the obtained tracts relative to the center of the ILF. Finally, Gomez et al., 2015 found a structure-behavior relationship between these functionally defined white matter tracts microstructural proprieties and performances of developmental prosopagnosia patients on the Benton Facial recognition test. However, this structure-behavior relationship was not present in the ILF (Gomez et al., 2015). **Gilles de la Tourette syndrome :** Thomalla et al., 2014 derived tractography from a Go/NoGo fMRI paradigm in Gilles de la Tourette's syndrome patients. To do so they closely monitored the tics during data acquisition by combining surface electromyogram and facial video recording. They ran a single seed region probabilistic fiber tracking from the activated left primary motor cortex (note that the issues related to single seed fiber tracking are covered elsewhere in the scoping review). Their result shows no difference between groups in the structural connectivity profile of the left primary motor cortex. The absence of difference between group in the structural connectivity profile could be attributable to this choice instead of using whole-brain or multiple seed tractography.

Post stoke aphasia: Three studies investigated post stroke aphasia (Griffiths et al., 2013; Scaccianoce et al., 2016; Xing et al., 2018). Griffiths et al., 2013 seized activation clusters of a syntactic processing task from a previous fMRI study (Tyler et al., 2010) and used these as seed regions in aphasic patients (note that the issues of acquiring fMRI data obtained from a different sample than dMRI data is covered elsewhere in the scoping review). They found that structural disconnection of either the ventral or dorsal language processing stream (Hickok and Poeppel, 2004) was associated with syntactic impairment in patients who completed offline (outside the scanner) syntactic processing tasks. Scaccianoce et al., 2016 first dissected the left arcuate fasciculus (AF) and the left cingulum bundle (CB) through a standard anatomical procedure (Catani and Thiebaut de Schotten, 2008). They then filtered the track using regions of interest (ROIs) derived from their fMRI covert verbal fluency task. This procedure was done on a healthy individual sample; however, they demonstrate that this procedure could be applied in a clinical context. To do so, they did a 3-month follow-up of an aphasic patient with three MRI sessions. They showed that the volume of connections (the volume the intersection of the track and the ROIs) changed across time. Xing et al., 2018 first mapped the brain network involved in picture naming of healthy individual using fMRI. They then used the peak activation regions as seed regions for fiber tracking. Once they had delineated the tracts, they imported binary mask of these tracts into aphasic brain dMRI data to verify which of these tracts were crucial for picture naming by conducting partial correlation between white matter microstructural properties (FA) and patients picture naming performances on the Philadelphia Naming Test (PNT). Their study identifies 14 tracts significantly related to patient's picture naming performances. The authors warn us that the tractography results obtain from healthy individuals may not directly reflect the true organization of stroke patients white matter (Xing et al., 2018).

Schizophrenia: Two studies investigated schizophrenia (Leroux et al., 2015; Wu et al., 2014) . Wu et al., 2014 used diffusion spectrum imaging (DSI) to track the dual stream of language and measured its microstructural proprieties in schizophrenic patients. They used an anatomical brain atlas to create their tractography seed regions. However, they chose these seed regions based on the MNI coordinate reported in Saur et al., 2008 fMRI experiment. They adjusted size and location of the seed region until the reconstructed tracts were consistent with a reference DTI atlas. The latter appears problematic because it is a post-hoc procedure that confirms their expected tractography result. However, their result shows a decreased of generalized fractional anisotropy (GFA) in the left ventral, right ventral and right dorsal tracts of schizophrenic patients. Leroux et al., 2015 performed inter hemispheric tractography between homotopic temporal brain regions activated by a verbal comprehension task in schizophrenic patients and controls. They report that patients with schizophrenia had lower GFA values compared to controls in the dissected interhemispheric callosal fiber. These values were associated with reduced hemispheric specialization for language in patients with schizophrenia (Leroux et al., 2015).

Multiple sclerosis: Two studies investigated multiple sclerosis (Bonzano et al., 2009; Wahl et al., 2011). Bonzano et al., 2009 performed fMRI-guided fiber tractography of the fronto-parietal attention network in multiple sclerosis patient's brain. A control group had performed the Paced Visual Serial Addition Test (PVSAT) in the fMRI and they derived their seed region for fiber tracking from the activated brain regions. They found that patients who had higher FA values in the investigated tract (superior longitudinal fasciculus) had brain activations patterns similar to controls. In contrast, the

patients with lower FA values in this tract showed bilateral cortical activations (Bonzano et al., 2009). Wahl et al., 2011 measured the micro structural proprieties of the motor callosal fiber in early relapsing-remitting Multiple Sclerosis patients. They placed a rectangular seed region on the bilateral motor hand knobs localized by a fMRI left/right-hand flexion paradigm then performed interhemispheric fiber tracking. Their study highlights that early relapsing-remitting Multiple Sclerosis patients show reduced FA values in the motor callosal fiber when compared to controls (Wahl et al., 2011).

Temporal lobe epilepsy: Two studies investigated temporal lobe epilepsy (TLE) (Powell et al., 2007; Riley et al., 2015). Powell et al., 2007 used a verb generation and reading fMRI task to investigate the impact of unilateral TLE on the structural and functional asymmetrical organization of the language network. Their participants were seven left TLE and seven right TLE. They used the functional activation as starting points to perform single seed fiber tracking procedure to reconstruct the white matter pathways underlying the language network (note that the issues related to single seed fiber tracking are covered elsewhere in the scoping review). Their finding indicates that left TLE patients had more symmetrical language activations, increased right hemisphere and reduced left hemisphere structural connections while controls and right TLE patients had a similar functional and structural leftward organization of the language network. Riley et al., 2015 studied the influences of the side of seizures on face processing functional and structural networks in unilateral TLE. To do so they performed fiber tracking between functional regions that showed altered brain activation when compared to controls. Their result demonstrates that the occipital face area and anterior temporal lobe are connected via the inferior longitudinal fasciculus and that individuals with TLE showed reduced mean FA along this tract suggesting a reduced structural integrity.

Alzheimer's disease: Two studies investigated Alzheimer Disease (AD) (Gao et al., 2014; Preti et al., 2014). Gao et al., 2014 recruited 13 healthy young adults, 13 healthy older adults and 17 patients with AD who completed a prospective memory task during fMRI data acquisition. The activated brain network among the whole sample was used as ROI for fiber tracking. They classified the resulting streamlines as “short-range fibers” if they had a maximum length of 35 mm and streamlines longer than that were classified as “long-range fibers”. Finally, they performed analysis of the microstructural propriety over these two types of fibers to identify potential differences across the groups. Their result indicates that when compared to younger adults, both older adults and AD patients had higher mean MD and lower mean FA in short-range fibers while only the AD patients had higher mean MD in long-range fibers. These results suggest that normal aging only affect short-range fibers while neurodegenerative disease processes such as AD are more prone to affect short and long-range fibers leading to greater cognitive deficits. Preti et al., 2014 performed whole-brain tractography in healthy elderly adults, mild cognitive impairment (MCI) participants and AD patients. They then filter out the track according the activated brain region involved in a verbal fluency task of each groups respectively. Finally, they measured the involvement of classical fiber bundle (i.e. arcuate fasciculus, cingulum bundle) in the verbal fluency task by calculating the overlap of the selected track with the classical fiber bundle defined by an anatomical atlas. They showed that MCI participant recruited extended verbal fluency functional network while AD patients recruited fewer brain regions when compared to healthy elderly adults. Their study also highlights that the left arcuate fasciculus and left cingulum

bundle of healthy elderly adults is more involved in verbal fluency followed by MCI participants than by AD patients who show reduced involvement of these fiber bundles in the verbal fluency.

Genetic syndrome: O'Hanlon et al., 2016 employs multimodal MRI approach to examine the structural and functional underpinnings of spatial working memory in individuals with 22q11 deletion syndrome. They performed whole-brain tractography then filtered out the track of interest using activated brain regions subserving a spatial working memory task. Their findings indicate that 22q11 deletion syndrome patients shows differences in white matter micro macro structural proprieties subserving working memory network (namely lower MD,RD and track volume in 22q11 when compared to healthy controls).

Scanner Parameters

Most studies (68%) employed 3 Tesla field strength scanners for data acquisition and only two studies (Jeon et al., 2014; Mazerolle et al., 2010) acquired high field MRI data (Supplementary figure 1A). The proportion of studies that had acquired MRI data on 1.5 Tesla scanners -this field strength is more common in clinical settings- were roughly similar across studies that had investigated patients (28%) or healthy individuals (26%).

Tractography specifications

A significant number of published articles (44%) who ran a probabilistic fiber tracking algorithm seeded 5000 streamlines per seed voxels. This is probably because it is the default parameters implemented in FMRIB diffusion toolbox (FSL; www.fmrib.ox.ac.uk/fsl). Descriptive statistics about the number of streamlines generated per seed regions are depicted in supplementary table 1. Concerning this particular topic, note that Gauvin et al. 2016 addressed the following question, "How many streamlines are needed to reliably compute volume or spatial extent of a bundle?" and concluded that it was variable from bundle to bundle depending on their "geometrical properties and ease of tracking particularities" (Gauvin et al., 2016).

Supplementary table 1: Number of streamlines generated per seed region descriptive statistics

	Mode	Mdn	Mean	SD	Min	Max
Streamlines per seed voxel	5000 (N=22)	5000	14081	327525	33	1000000

fMRI experimental designs

Note that 71% of the fMRI experimental design used were blocked while 21% of studies used event-related fMRI. A remaining 8% of studies did not clearly specify which fMRI design they used (Supplementary figure 1B).

Other methods used to derive seeds/filter region from task-based fMRI.

Two articles positioned a cubic or rectangular seed region near or covering brain regions activated by a task (Lemaire et al., 2013; Wahl et al., 2011). The latter is similar to the sphere method except cubes were not necessarily centered on the peak fMRI coordinate. Guye et al., 2003 seeded their fiber tracking from a set of three voxel located in the white matter immediately adjacent to the highest significantly activated fMRI voxel. Brauer et al., 2011 launched their tractography from a single 3mm isotropic voxel that was located on peak fMRI activation. Szczepanski, Pinsk, Douglas, Kastner, &

Saalmann, 2013 created their seed regions by selecting the six voxels that surrounded the fMRI peak activation coordinate. Again, this last method is fairly similar to the sphere approach except that the size of the seed region is determined by the voxel size and the number of voxels chosen.

Other methods used to address the gray/white matter boundary

Anderson et al., 2012; Ethofer et al., 2012; Oechslin et al., 2017 visually inspected if their ROIs were in contact with white matter or made sure that it was in brain regions where FA > 0.2. (Gomez et al., 2015; Kleiser et al., 2010; Staempfli et al., 2008) created spherical ROIs of a size that guaranteed contract with white matter (ranging from 3mm radius to 7mm radius). Morgan et al., 2009 and Wahl et al., 2011 lowered the fiber tracking termination threshold between FA >0.15 and FA >0.1 to insure tracking reaches the grey matter where FA is generally less than 0.2 (fiber tracking is generally performed in area where FA > 0.2). Scaccianoce et al., 2016 first performed whole-brain tractography. Then extended both extremities of their tracts of interest of 10 mm length using a in-housse MATLAB script. Finally, they filtered the track using regions of interest (ROIs). Kim & Kim, 2005 added at least one more voxel beyond the gray/white matter boundary into their seeding ROIs.

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FIGURE LEGENDS

Figure 1: Schematic representation of the types of MRI modalities combination

Figure 2: PRISMA Flow Diagram for Scoping Review

Figure 3: (A) Number of studies that collected fMRI & dMRI data published per year sorted by combination types. (B) Repartition of studies that collected fMRI & dMRI data by combination types

Figure 4: Number of studies included published and their sample size sorted by the type of population investigated.

Figure 5: (A) Repartition of diagnosis across included studies (B) Repartition of the neuroscientific domain investigated

Figure 6: Number of studies included published per years sorted by microstructure modelling category.

Figure 7: (A) Repartition of tractography algorithm used across studies (B) Repartition of tractogram methods used across studies (C) Repartition of spaces used for tractography

Figure 8: (A) dMRI preprocessing software repartition. The category others represent the following softwares that were used by fewer than 3 publications; Camino, Diffusion and perfusion tools, DTIstudio, Philips PRIDE workstation, Slicer, PatXfer, Bear toolbox, ExploreDTI, MedINRIA, Trackvis and AFNI (B) Tractography software repartition. The category others represent the following software that were used by fewer than 3 publications: Camino, DTIquery, mrDiffusion, PatXfer, Slice, Bear Toolbox, DTIstudio and ExploreDTI. (C) fMRI software repartitions.

Figure 9: (A) Repartition of the methods to derive seed region from task-based fMRI. (B) Repartition of methods used to match the fMRI and dMRI spaces. (C) Repartition of the methods to address the gray/white matter boundary

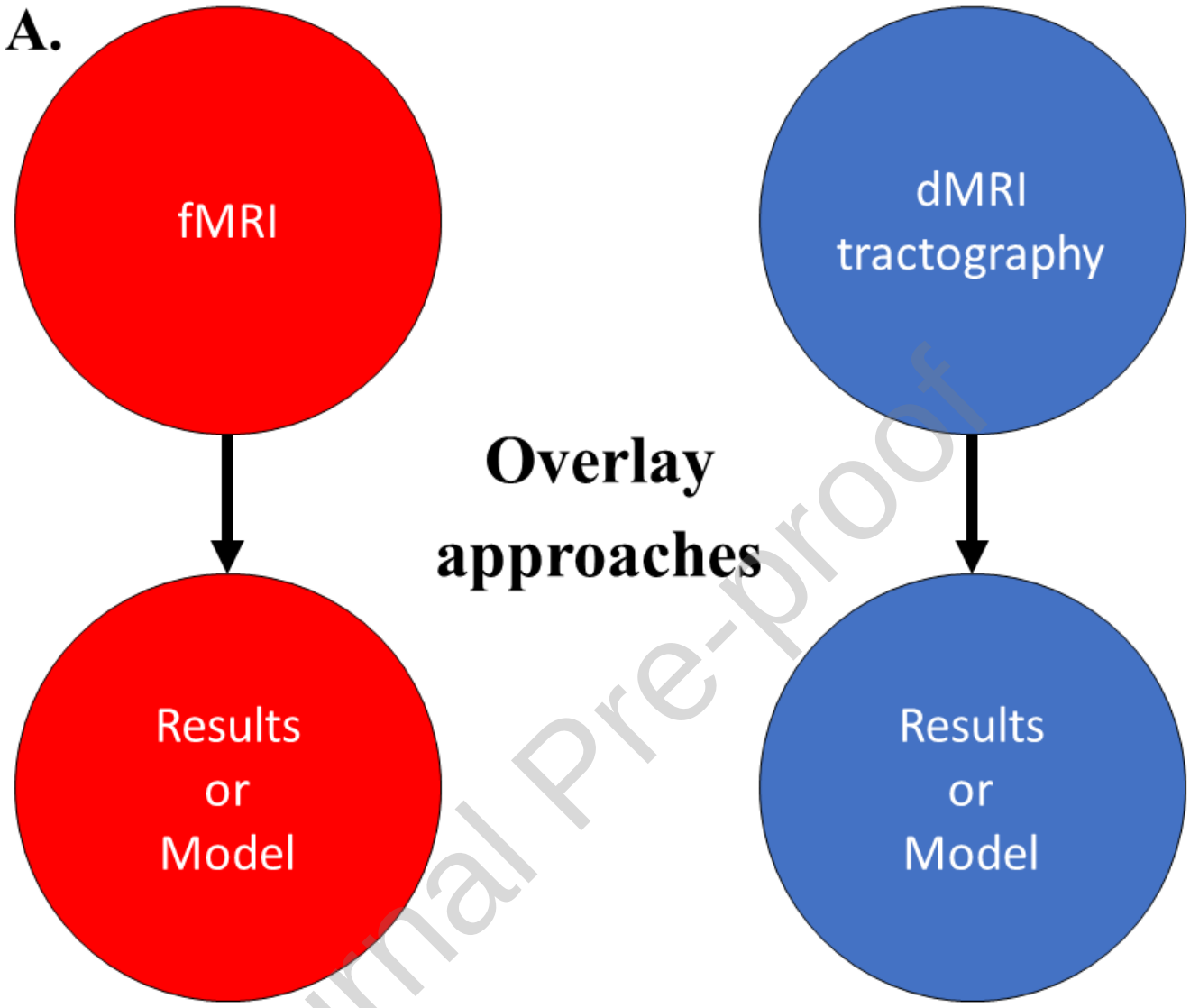
Figure 10: Two examples of functionally derived fibre tracking data from multiple participants integrated in a group statistic while remaining in the participants native space. **(A)** Summary of anatomical connections underlying visuospatial imagery found in the Whittingstall et al., 2014 study. Connections in red represent those observed in over 80% of subjects. Reprinted from Cortex, vol. 56, Whittingstall et al., Structural network underlying visuospatial imagery in humans, page 95, copyright 2013, with permission from Elsevier. **(B)** Left: Left hemisphere intraparietal sulcus topographic subregions (IPS1–4) connectivity to retinotopically defined striate and extrastriate visual regions. Right: Single participant illustrations of fiber tracking between IPS1 and V1. Reprinted from NeuroImage, vol. 82, Bray et al., Structural connectivity of visuotopic intraparietal sulcus, page 141, copyright 2013, with permission from Elsevier.

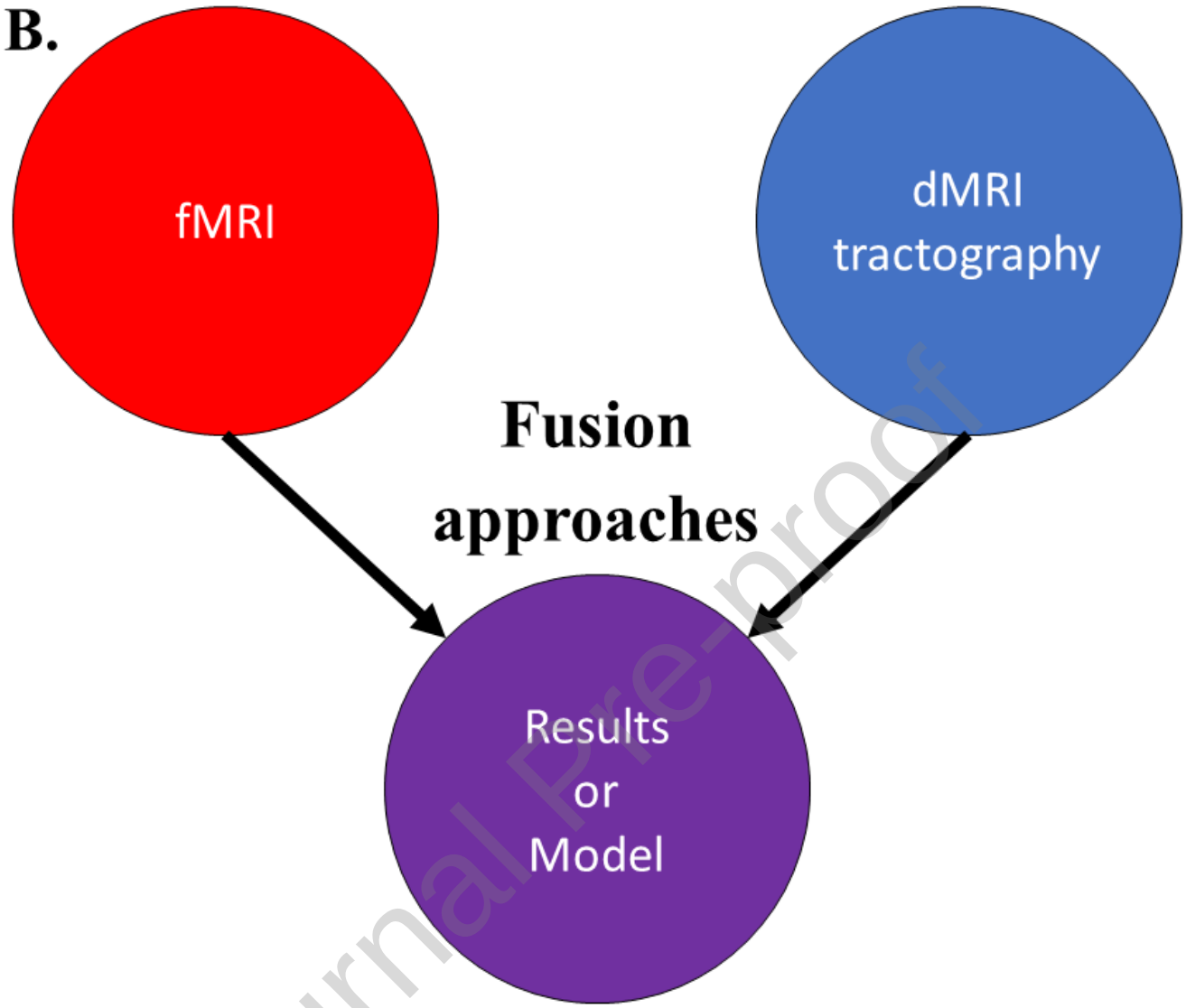
Figure 11: Two examples of structure to function relationship derived from the integration task-based fMRI results to guide fiber tracking while remaining in the participants native space. Correlations between the FA of a functionally defined white matter track and performance in face-processing tasks **(A)** (Benton Face Recognition task (BENTON) and **(B)** the Cambridge Face Memory Test (CFMT)) in developmental prosopagnosia patients (DPs) and Typical Adults from Gomez et al., 2015 study. Reprinted from Neuron, vol. 85, Gomez et al., Functionally Defined White Matter Reveals Segregated Pathways in Human Ventral Temporal Cortex Associated with Category-Specific Processing, page 223, copyright 2015, with permission from Elsevier.

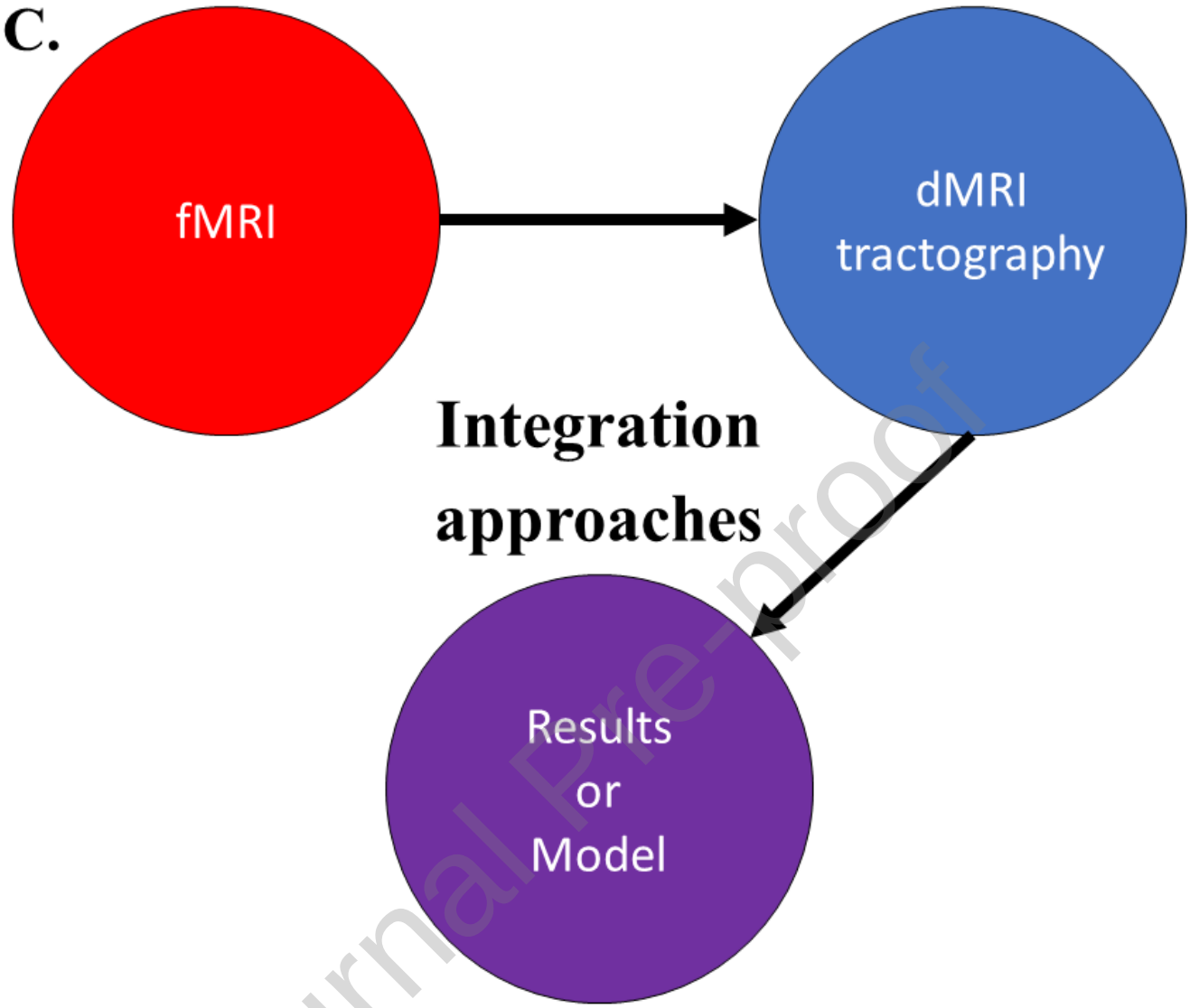
Figure 12: Two examples of methods used to represent fibre bundles obtained in the participants native space in a common space. **(A)** Group fascicles connecting right and left sound auditory cortexes via the corpus callosum overlaid onto the onto an averaged T1 weighted image in the MNI space. The signal color intensity is proportional to the number of participants in which the tracts were identified (2 to 13 participants). Reprinted from NeuroImage, vol. 84, Javad et al., Auditory tracts identified with combined fMRI and diffusion tractography, page 572, copyright 2013, with permission from Elsevier. **(B)** Each map shows the indices of connection probability between 2 cortical regions. The color intensity scales refer to the PIBI where higher values indicate higher probability that a voxel is connected by a direct path to both seed regions. The abbreviations refer to: arcuate and superior longitudinal fascicles (AF/SLF), middle longitudinal fascicle (MdLF), premotor node (PMd) and anterior temporal node (T1a). Reprinted from NeuroImage, vol. 49, Saur et al., Combining functional and anatomical connectivity reveals brain networks for auditory language comprehension, page 3193, copyright 2009, with permission from Elsevier.

Supplementary figure 1: (A) Scanner field strengths repartition. (B) fMRI experimental design repartition.

Supplementary Figure 2: Number of studies included published per years sorted by tractography algorithms.







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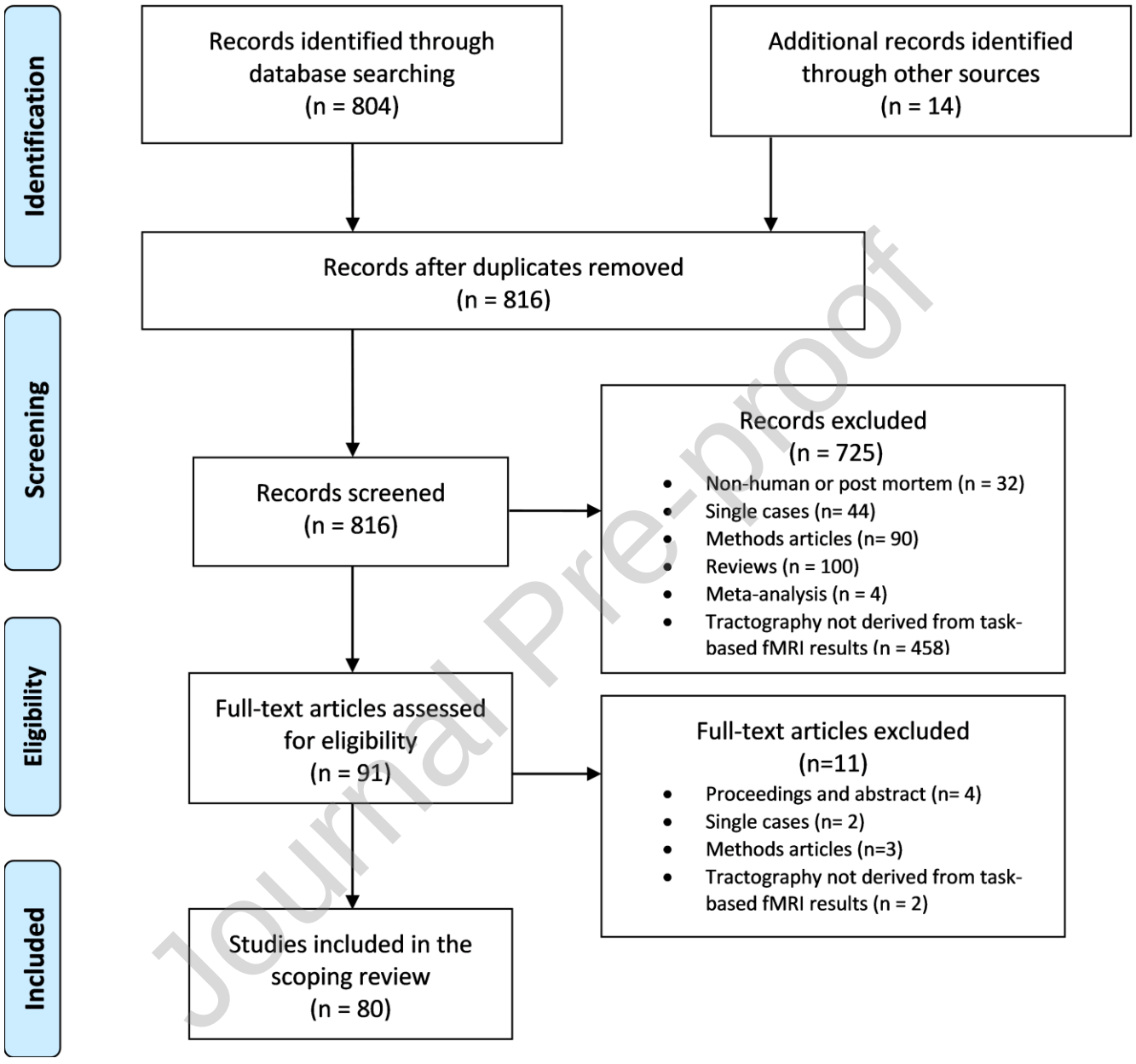

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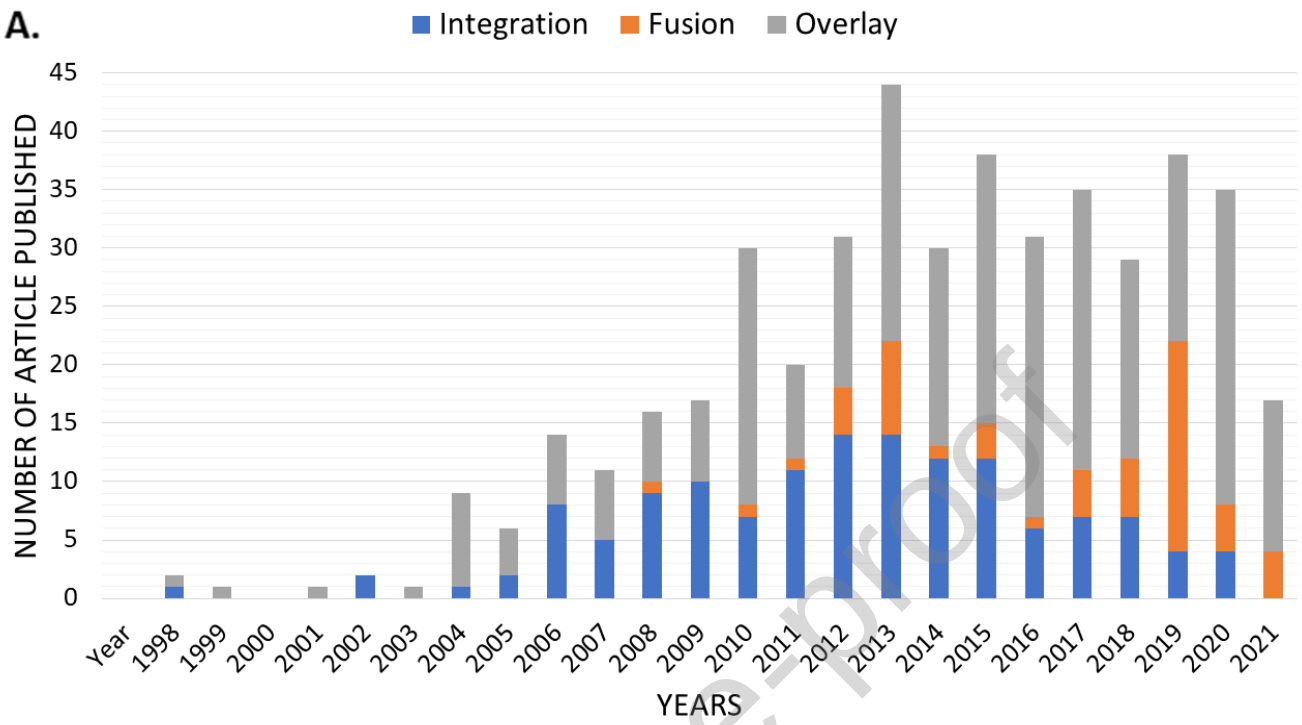

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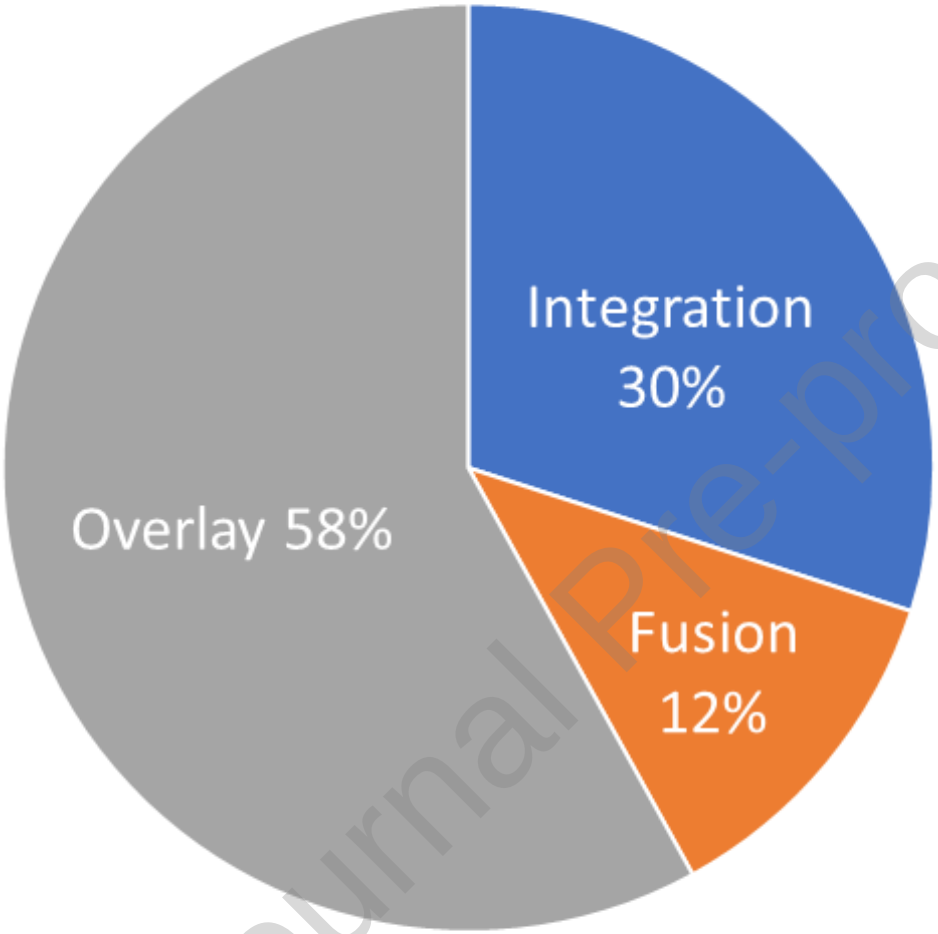

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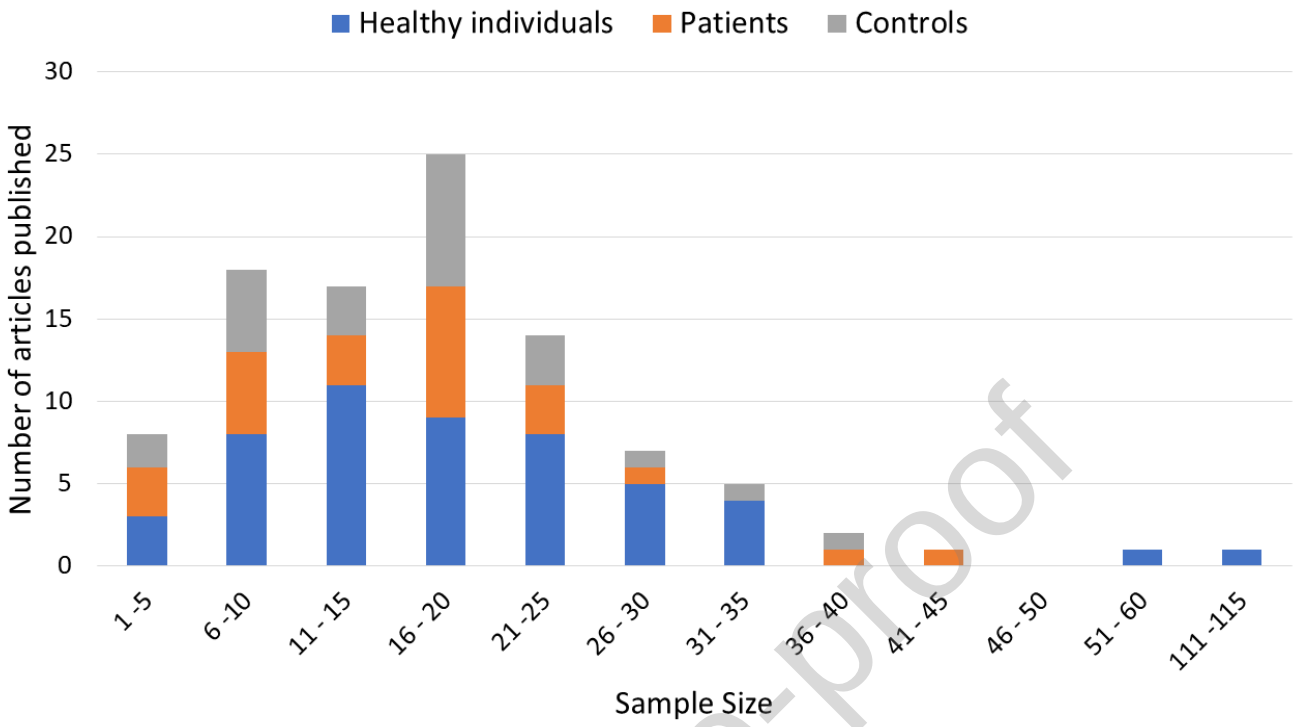

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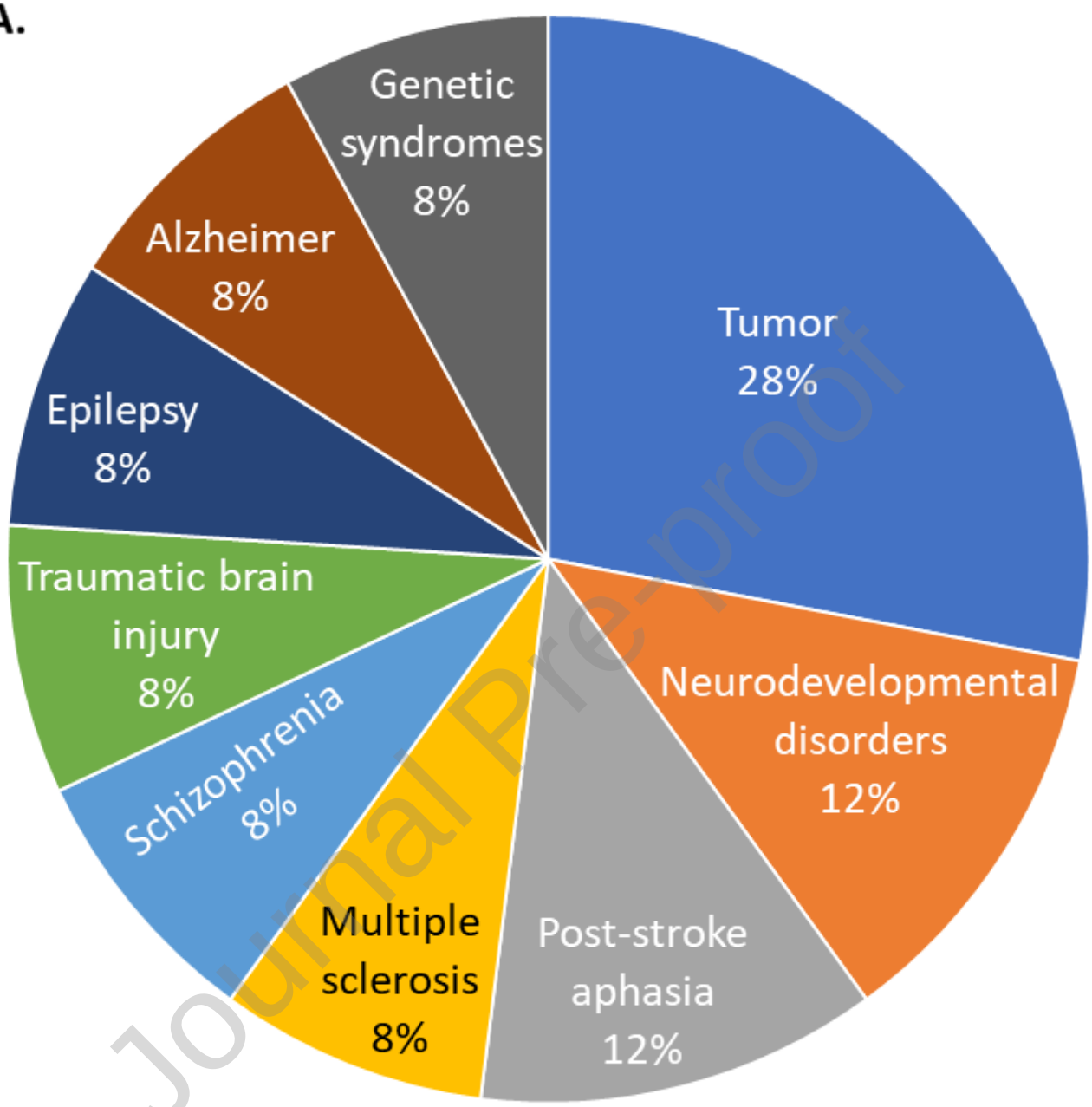

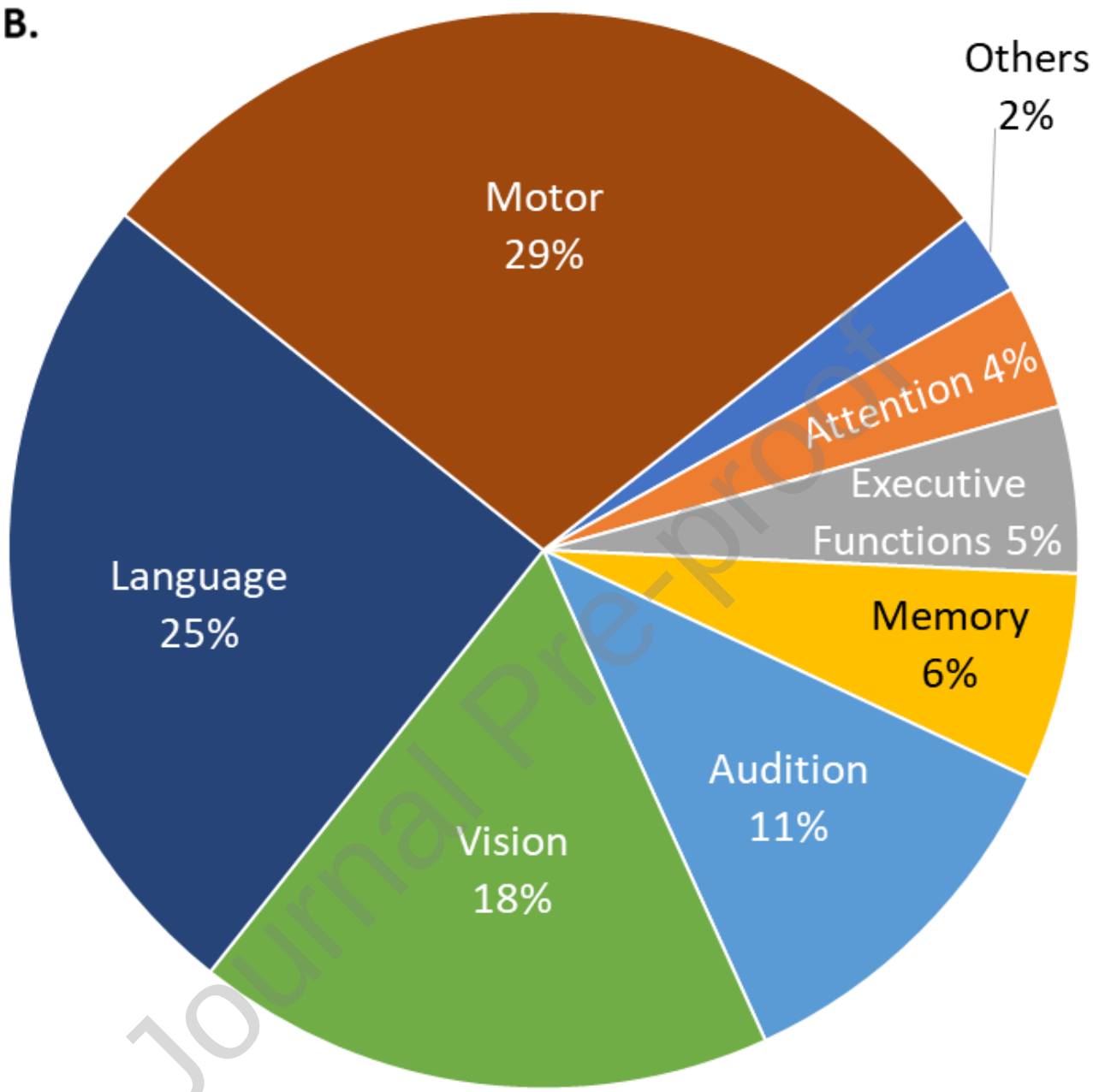

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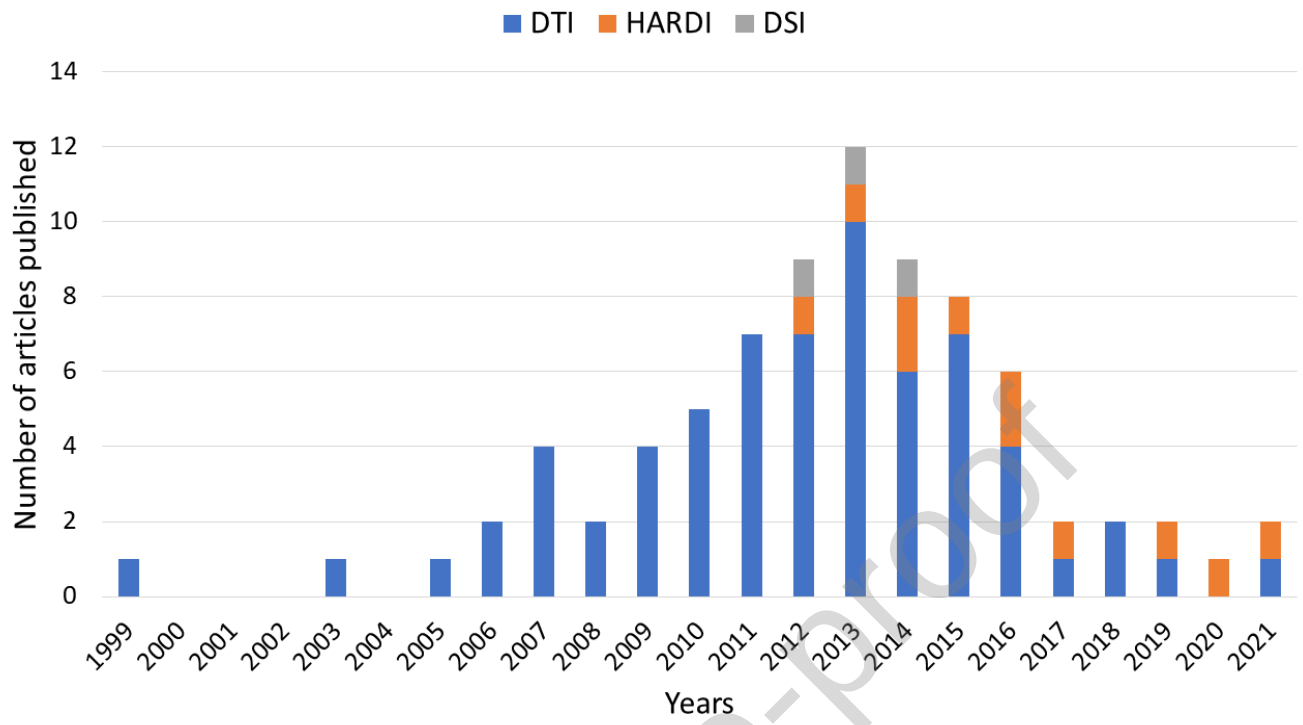

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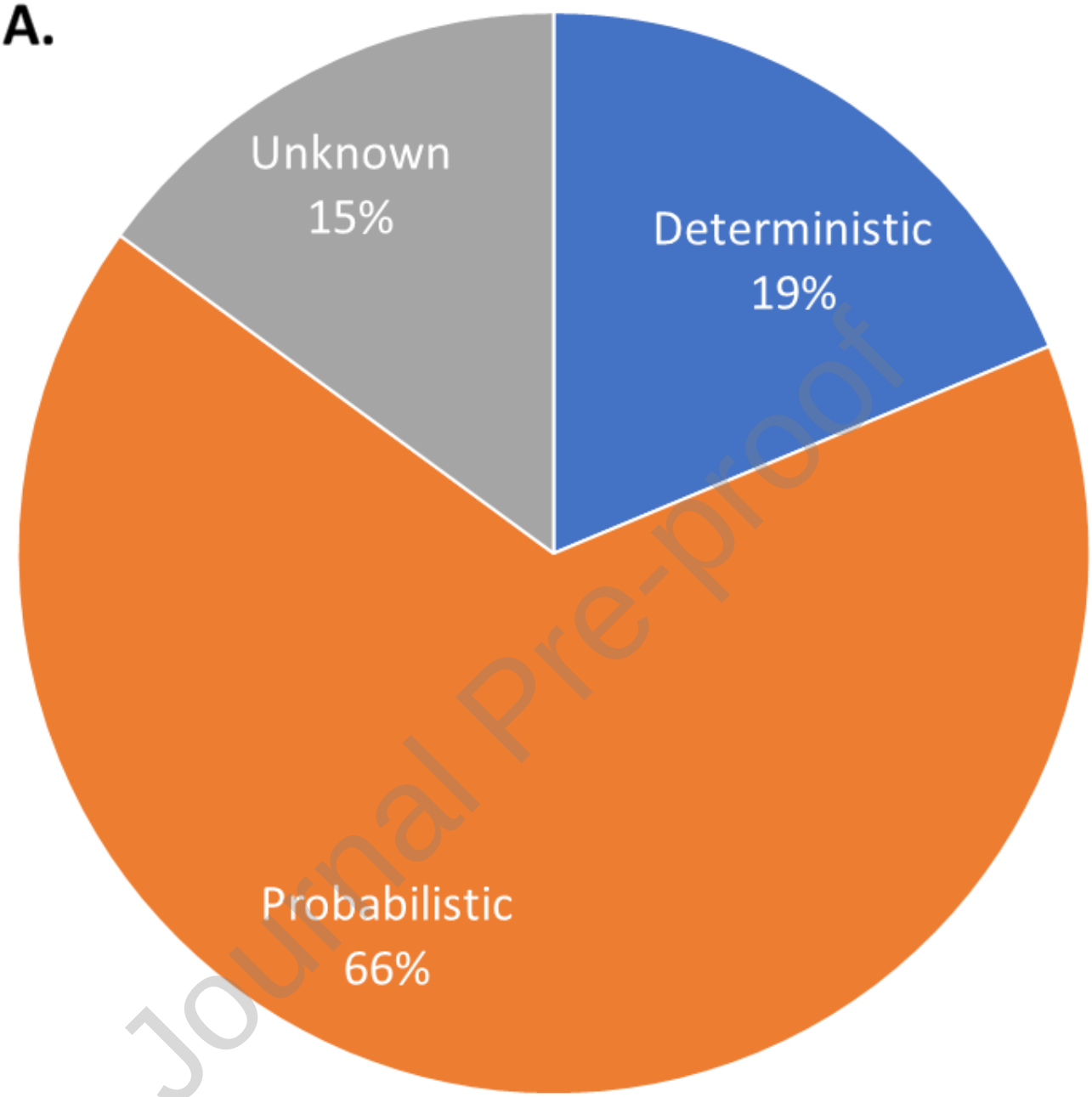

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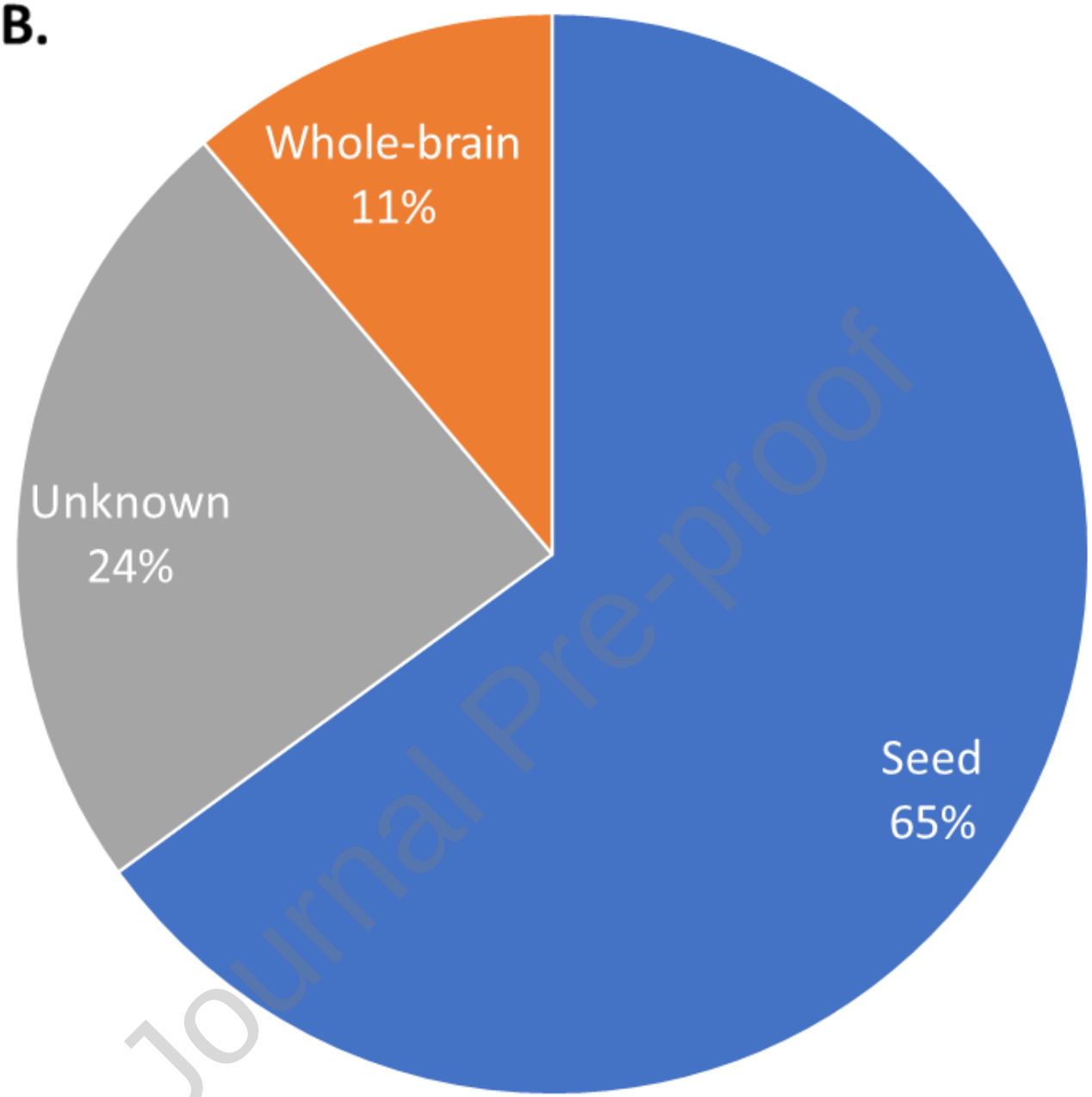

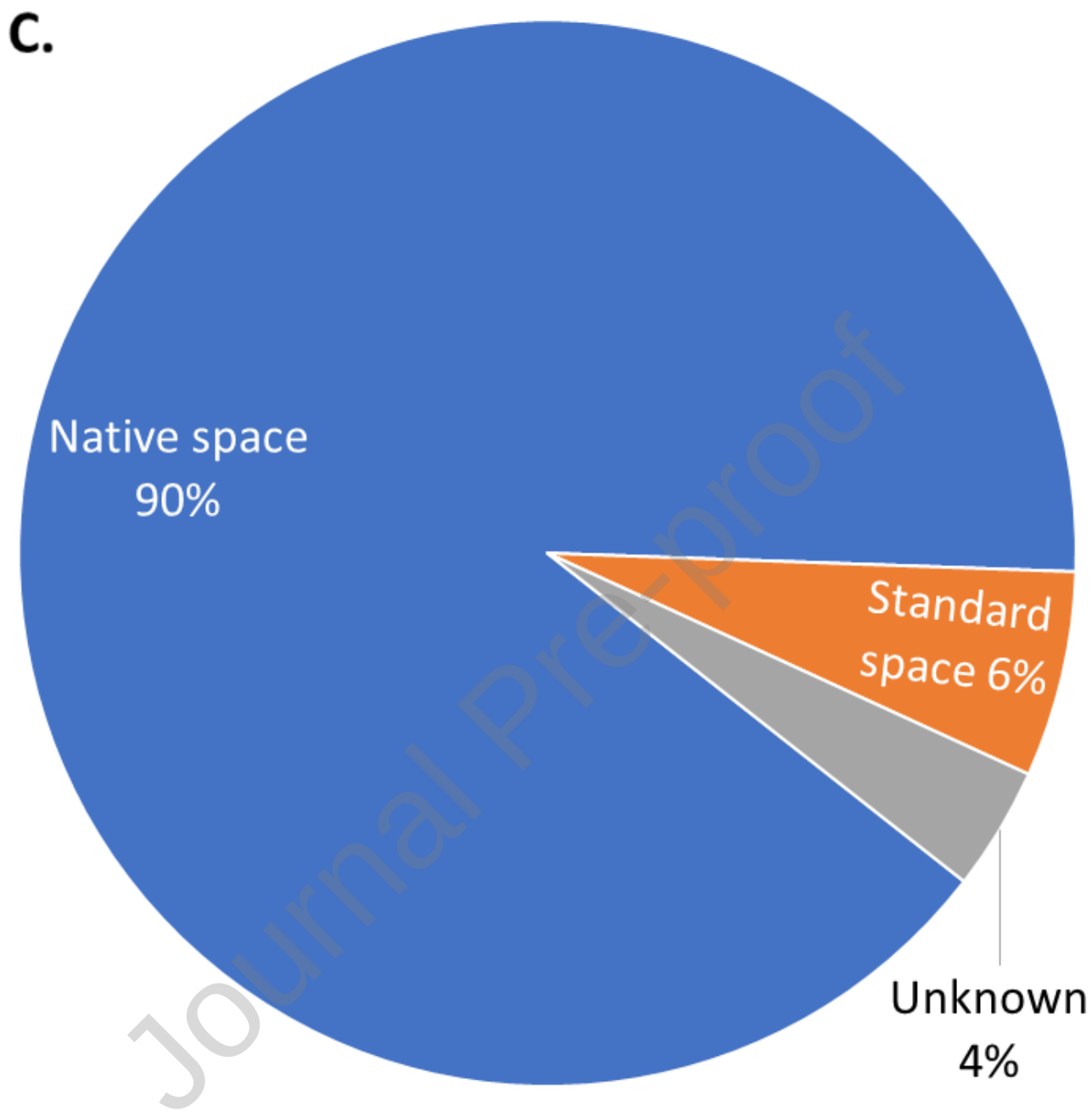

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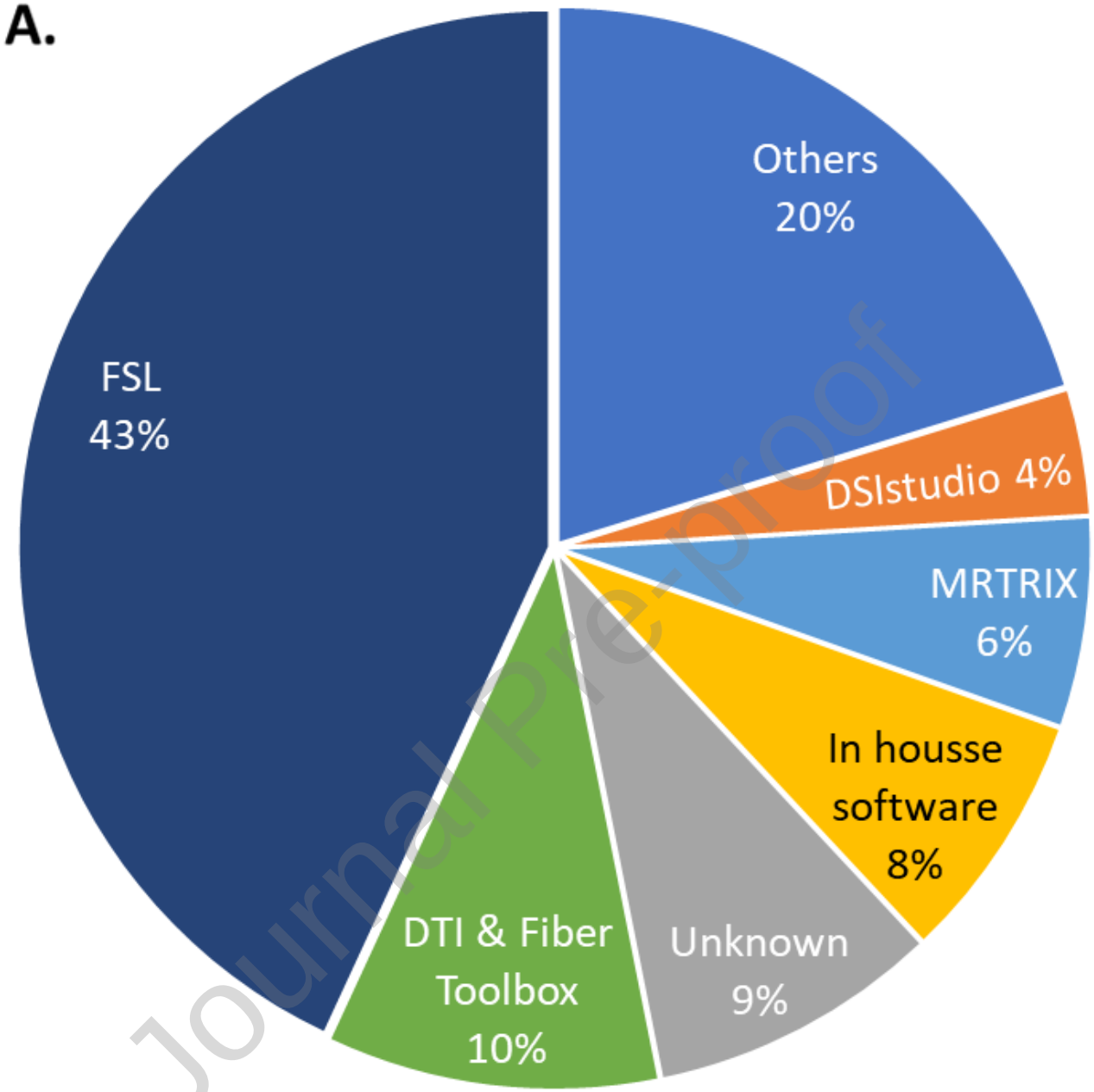

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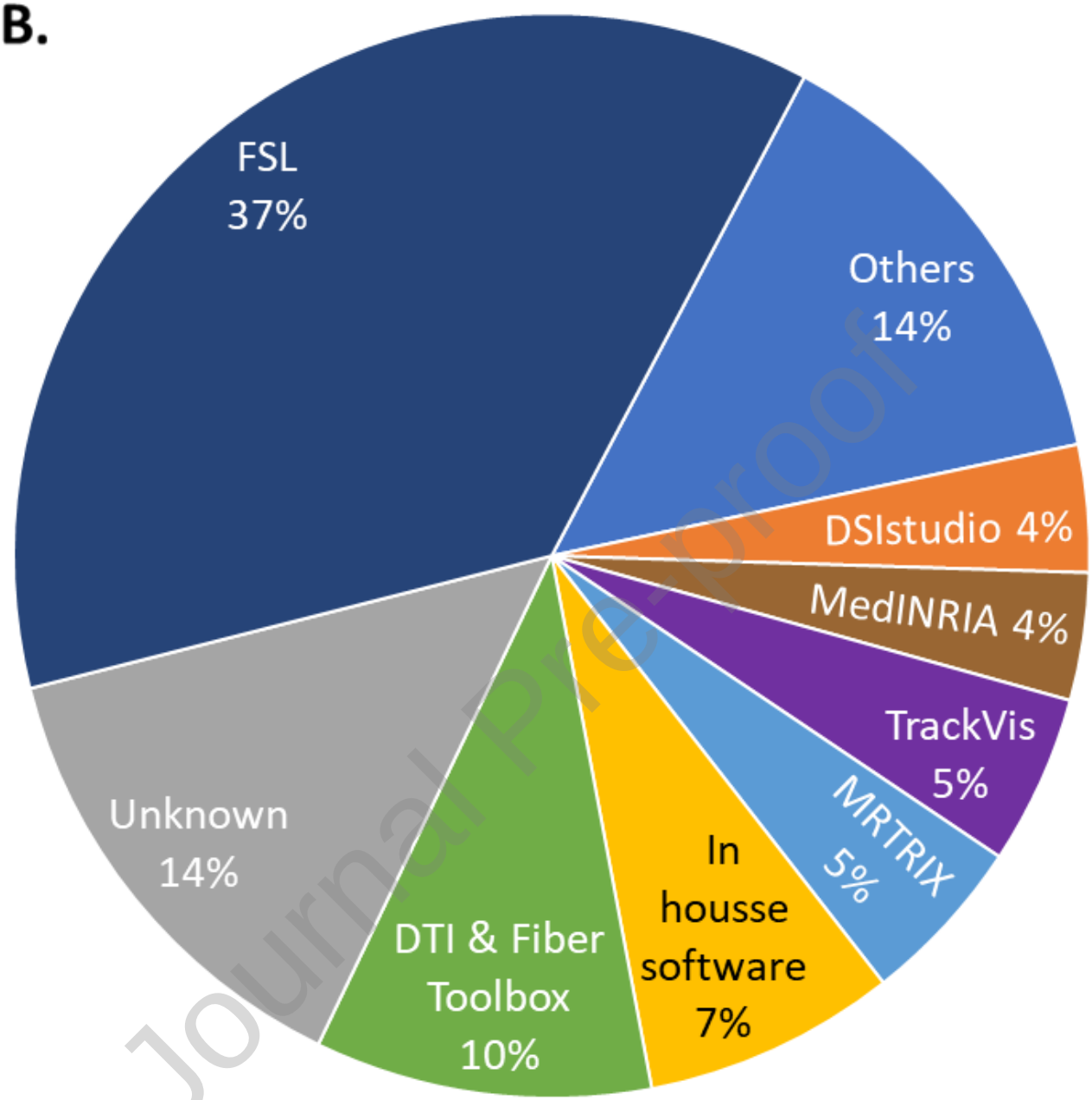

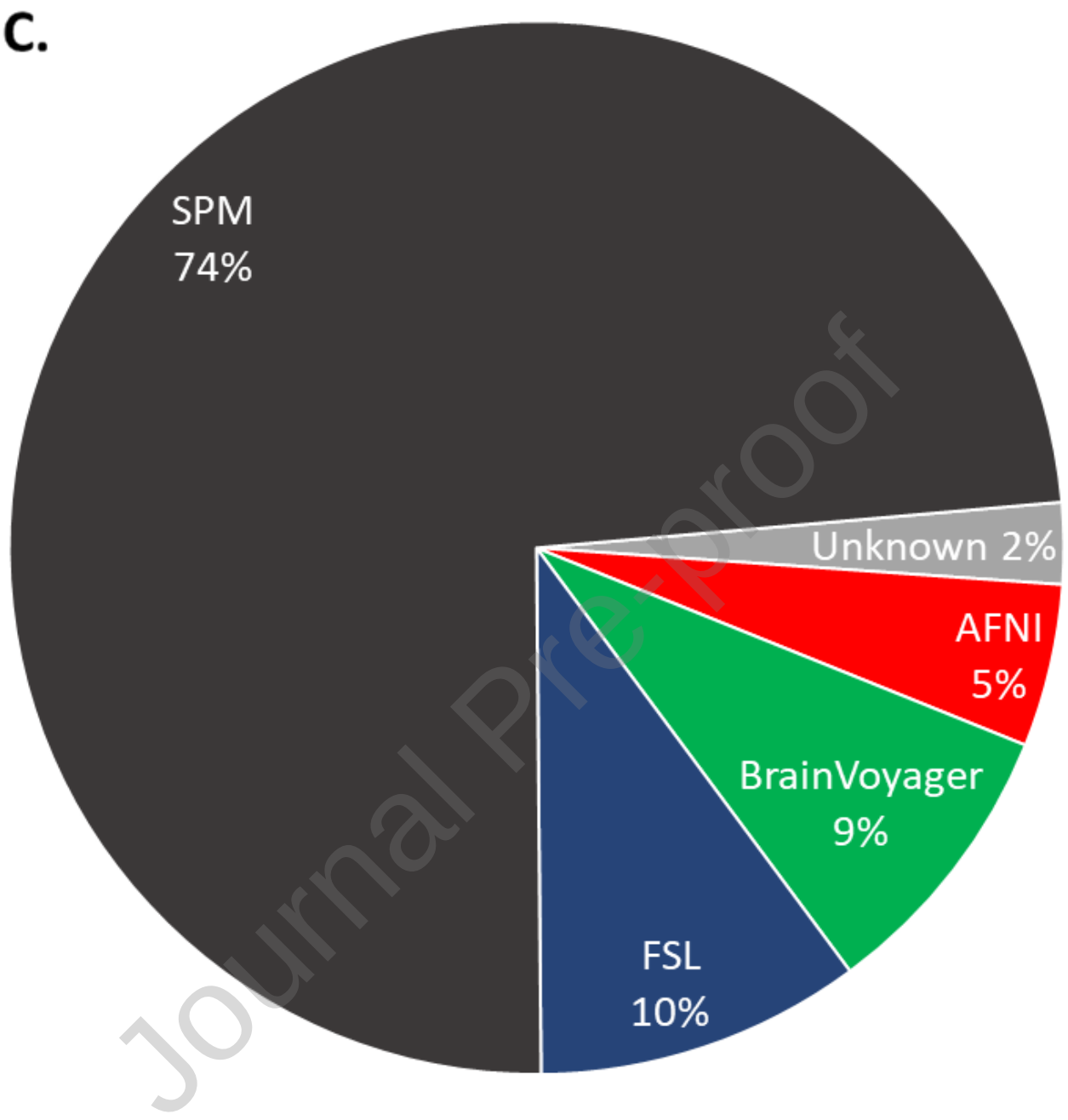

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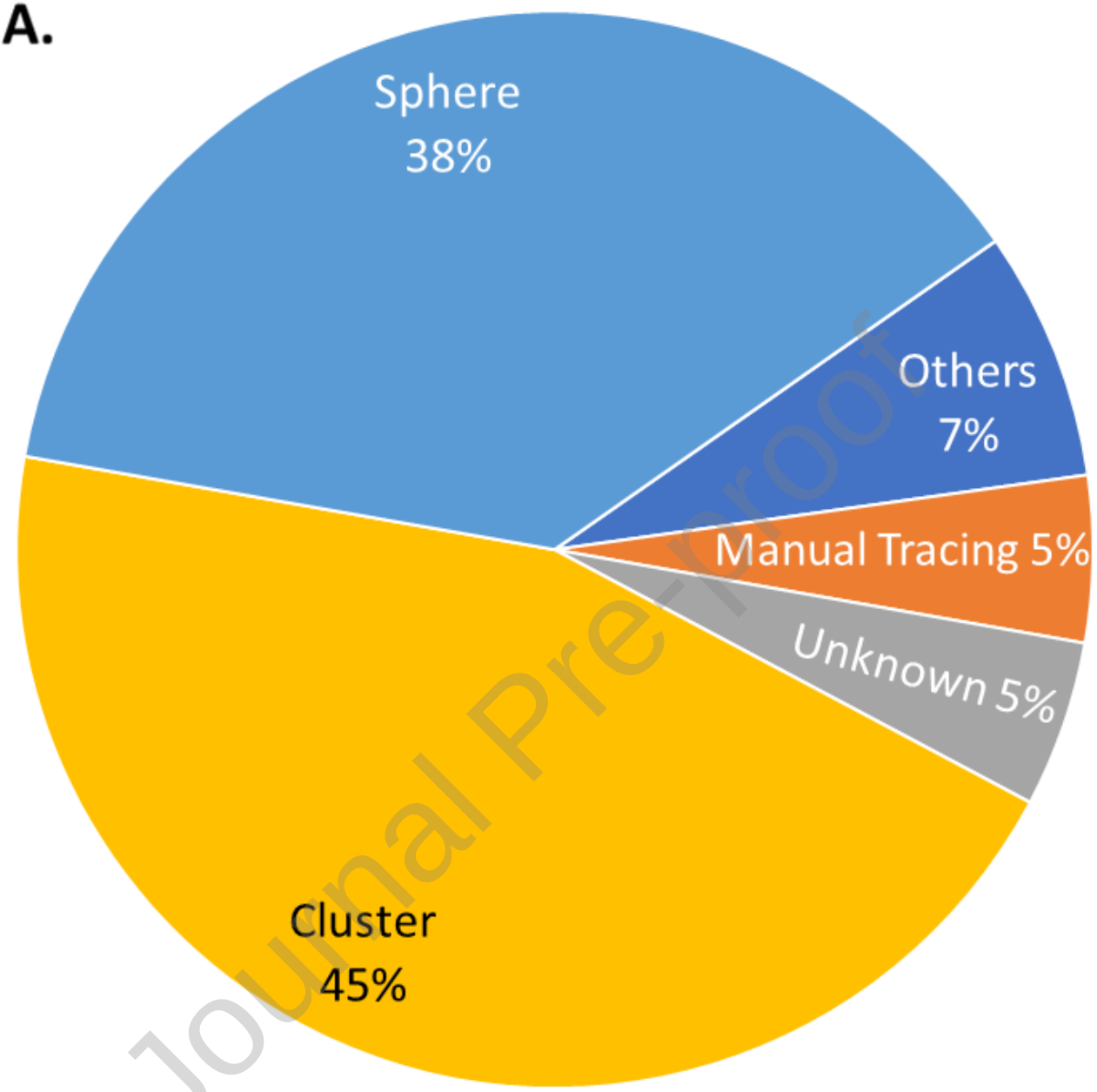

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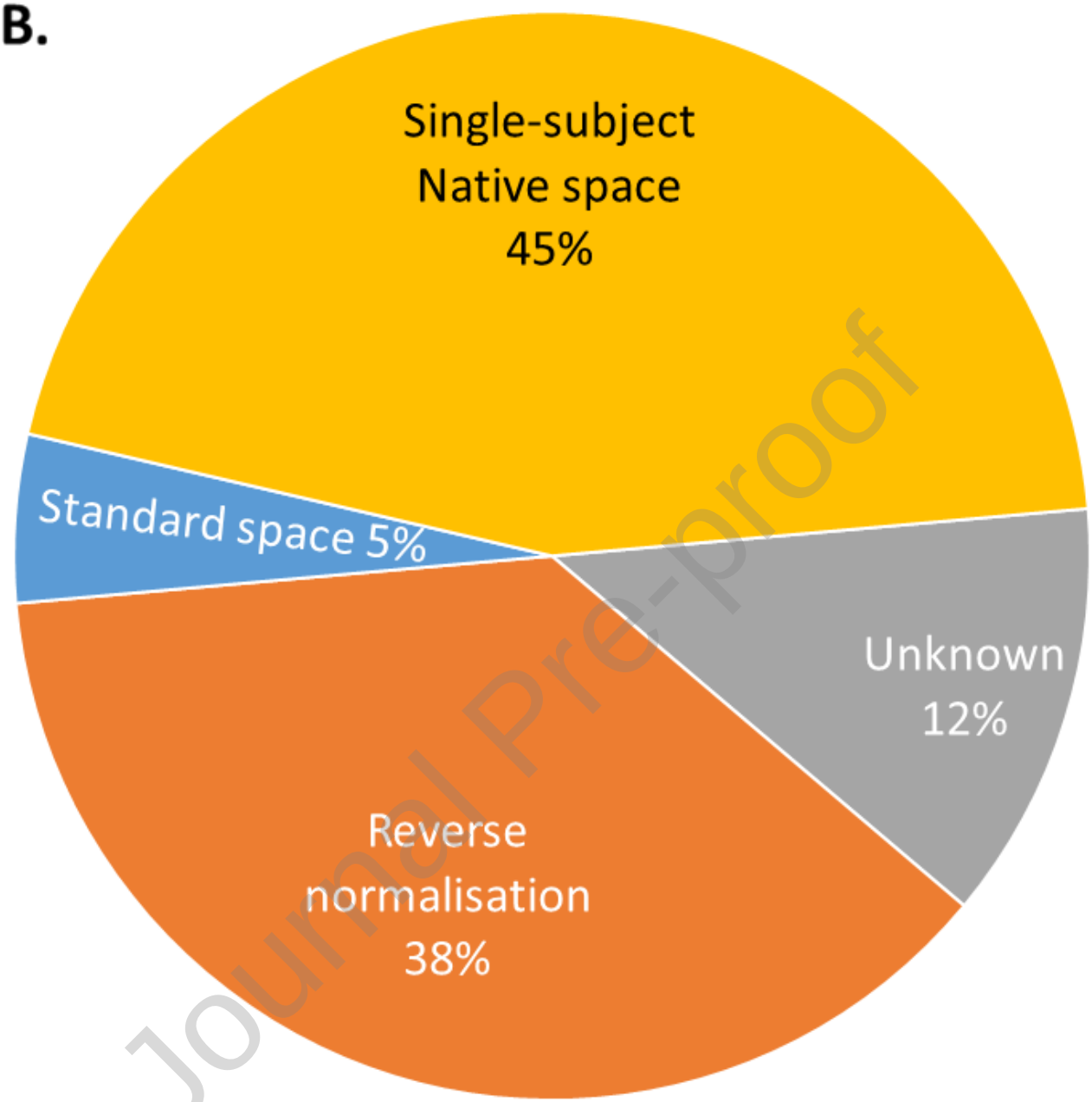

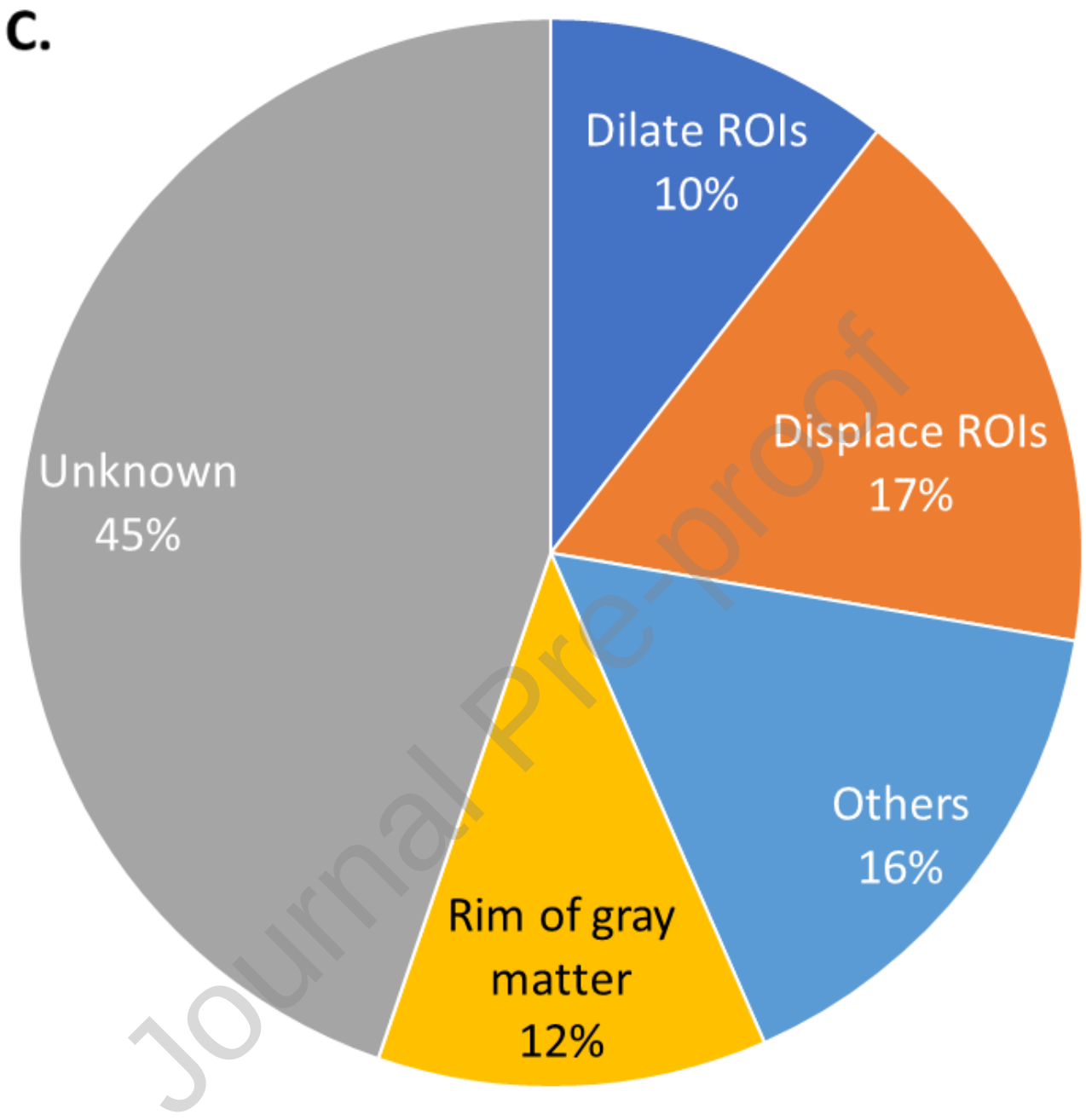

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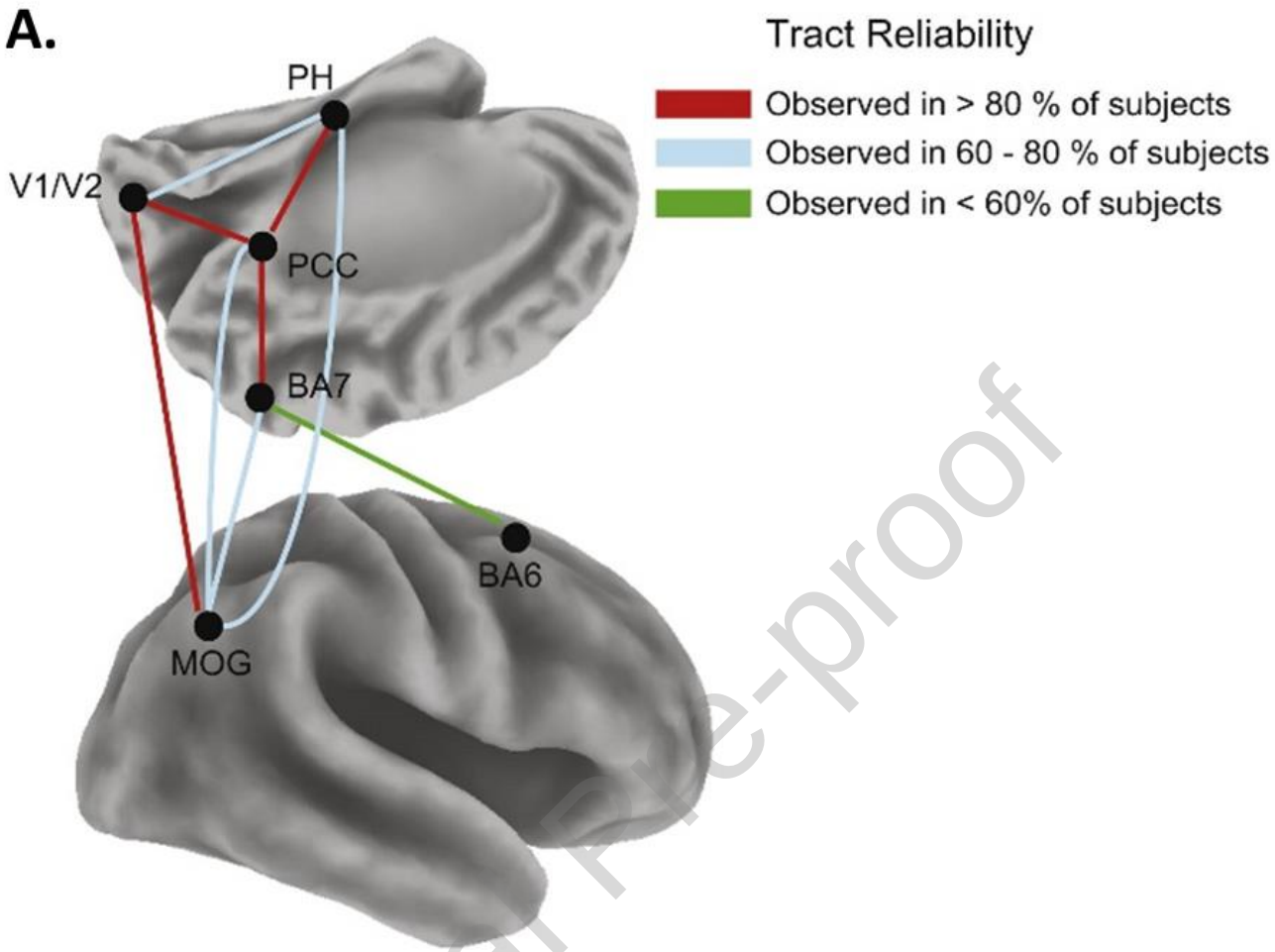

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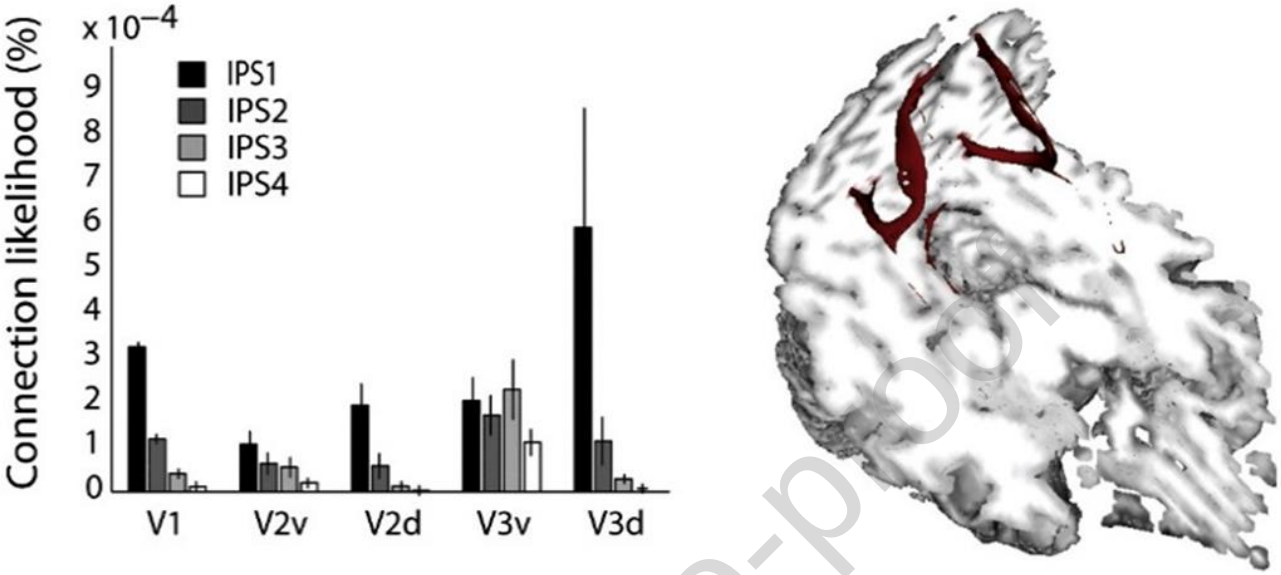

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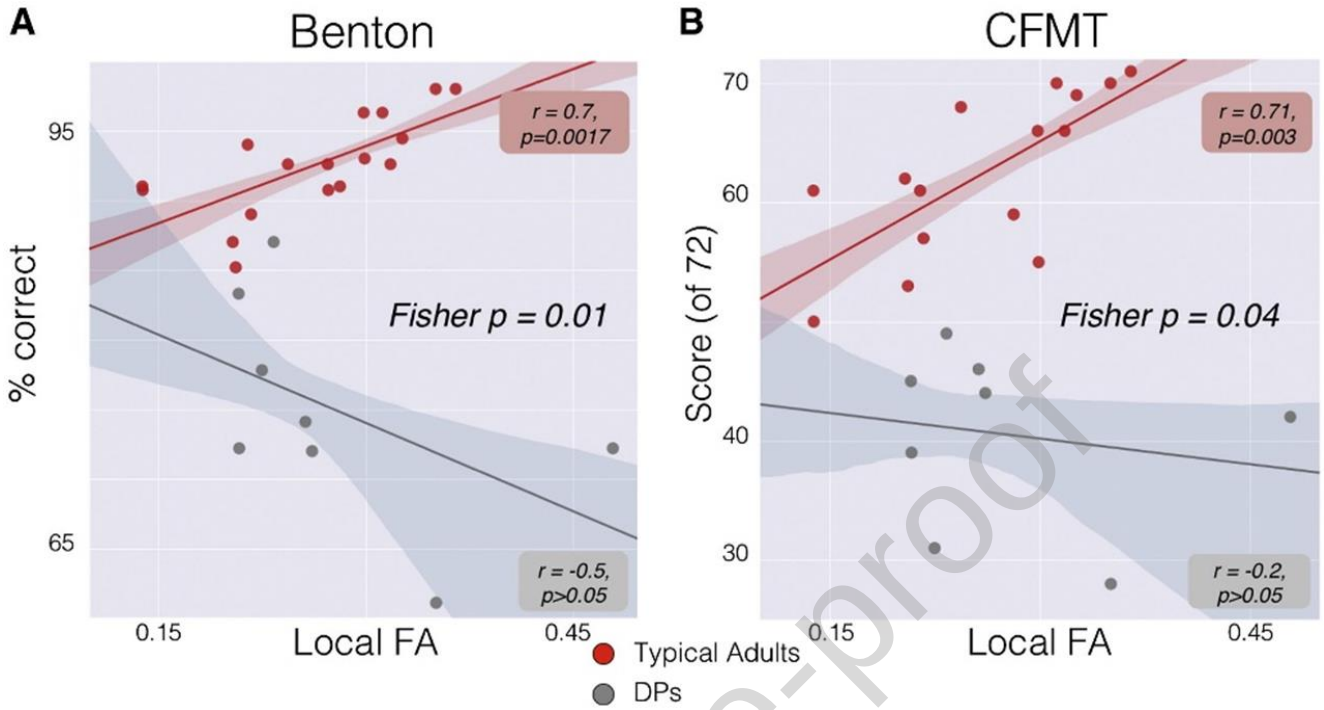

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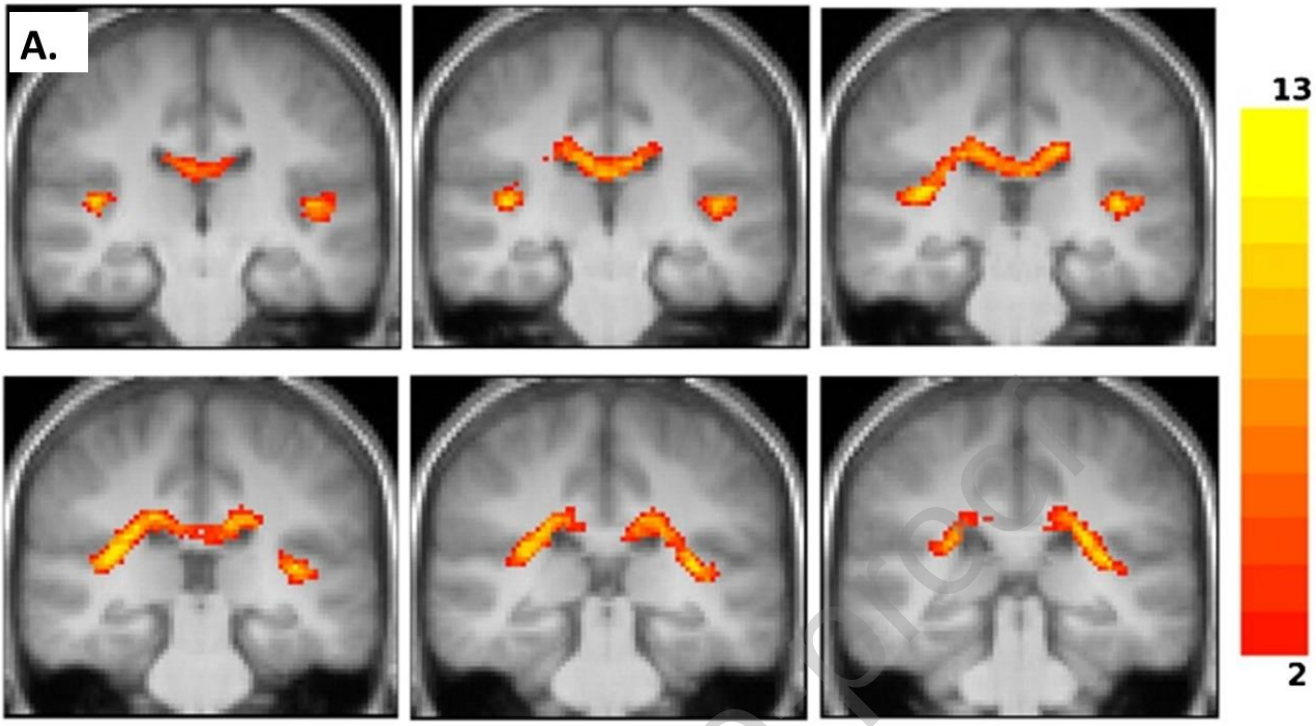

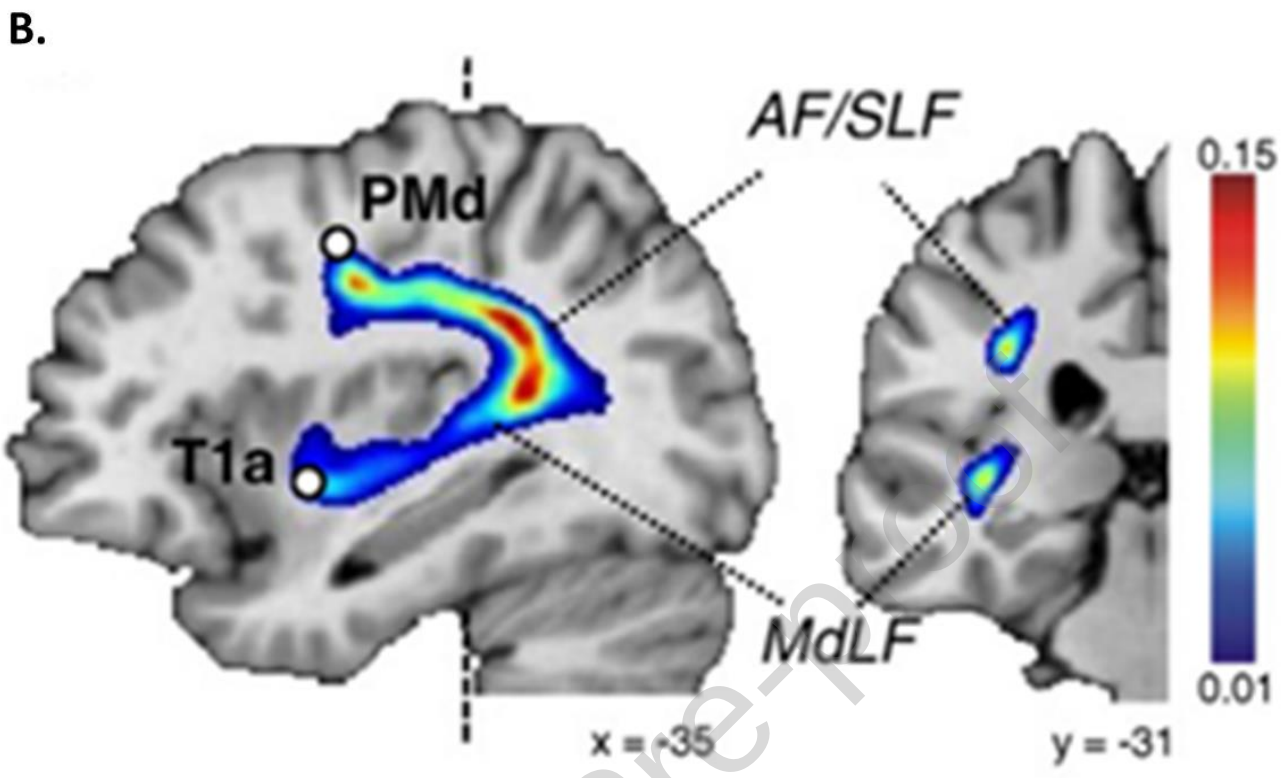

Figure-12

CREDIT STATEMENT

Julien Jarret : Conceptualization, Data Curation, Writing - Original Draft; Project administration
Arnaud Bore: Writing - Review & Editing, Methodology
Christophe Bedetti: Writing - Review & Editing, Methodology
Maxime Descoteaux Writing - Review & Editing, Methodology
Simona Maria Brambati: Conceptualization; Supervision

HIGHLIGHTS

• We reviewed 80 studies that integrated task-based fMRI to guide tractography over the last two decades • We present findings about the integration of task-based fMRI to tractography • It will help researchers to use this integrative multimodal MRI approach • We provide references pointing to best practices