Université de Montréal

Intégration de l'imagerie par résonance magnétique fonctionnelle (IRMf) à la tractographie pour cartographier les réseaux corticaux impliqués dans la dénomination d'images

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Résumé

Il est de plus en plus communément admis que la plupart des fonctions cognitives chez l'humain sont organisées sous forme de réseaux cérébraux distribués plutôt que strictement sous forme de modules anatomiques ségrégués et localisés. Parmi ces fonctions cognitives, nos capacités à nommer des objets ou à formuler des idées sont fondamentales dans la communication verbale et une perturbation de ces capacités peut mener à des limitations significatives au quotidien (ex. manque de fluidité, discours vide de sens, paraphasies et difficultés à se faire comprendre).

La combinaison multimodale des données en imagerie par résonance magnétique (IRM) est une façon d'étudier ces réseaux cérébraux. Elle permet d'investiguer simultanément plusieurs pans de l'architecture neurobiologique qui forme ces réseaux cérébraux (ex. les dynamiques fonctionnelles qu'entretiennent les différentes aires cérébrales et leurs connexions anatomiques sous-jacentes). L'intégration de l'IRM fonctionnelle (IRMf) pour guider la tractographie représente une combinaison multimodale pertinente pour étudier le réseau fonctionnel (aires cérébrales) et structurel (fibre de matière blanche) qui permet la dénomination d'images chez l'humain.

Néanmoins, la combinaison de ces modalités est complexe et il n'existe à ce jour aucune documentation strictement dédiée à l'intégration l'IRMf pour guider la tractographie (ex. procédurier, bonnes pratiques, etc.). Le premier objectif de cette thèse consistait donc à effectuer une synthèse intégrative des aspects méthodologiques associés à l'intégration de l'IRMf pour guider la tractographie via une étude de la portée (article/étude #1). Nos résultats sont organisés en 19 constats qui concernent les défis méthodologiques associés à cette méthode de combinaison multimodale. Nous y proposons également des recommandations, des pistes de solution et avons identifié des lacunes dans les connaissances associées à cette méthodologie.

Le second objectif de cette thèse visait à cartographier le réseau cérébral impliqué dans la dénomination d'images en intégrant l'IRMf pour guider la tractographie auprès de jeunes adultes en santé (article/étude #2). En appliquant les connaissances de l'article/étude #1 dans le cadre d'une étude empirique, nous avons pu proposer un modèle neurocognitif de la dénomination

d’images. Dans ce modèle, nous validons la présence d’une voie ventrale et dorsale du traitement de l’information. Les résultats suggèrent aussi que les parties postérieures du cortex inférotemporal et du gyrus temporal supérieur peuvent servir d’interface entre ces deux voies du traitement de l’information. Cette étude appuie également la suggestion d'une voie ventrale indirecte qui transige par le lobe temporal antérieur.

Finalement, cette thèse propose un outil fort utile pour les chercheurs qui désirent utiliser cette méthode intégrative, avancer les connaissances ou encore développer de nouveaux outils méthodologiques. Grâce à a l’intégration de l’IRMf pour guider la tractographie et la triangulation des données issues d’autres méthodes, cette thèse offre une analyse détaillée des processus cognitifs et des bases neurobiologiques impliqués dans la dénomination d’images. Il s’agit encore ici d’un outil très pertinent pour tous les cliniciens qui ont recours à la dénomination d’images dans le cadre de leur pratique.

Mots-clés : Imagerie multimodale, Imagerie par résonance magnétique, IRMf, tractographie, matière blanche, langage, dénomination d’images, étude de la portée

Abstract

It has become more and more consensual that most cognitive functions in humans are organized in distributed brain networks rather than simply segregated and localized modules. Amongst these cognitive functions, our ability to name objects and elaborate ideas is fundamental for verbal communication as naming impairments can lead to significant limitations (i.e., lack of fluidity, empty speech, paraphasias and struggles to be understood).

Multimodal magnetic resonance imaging (MRI) data combination provide opportunities for studying brain networks. It allows us to simultaneously investigate different aspects of the neurobiological architecture that forms brain networks (i.e., the functional dynamics that brain areas maintain together and their underlying anatomical connections). The integration of functional MRI (fMRI) to guide diffusion MRI (dMRI) tractography therefore represents an interesting way of combining multimodal MRI to study functional networks (brain areas) and white matter structures that allow picture naming abilities in humans.

However, combining different MRI modalities remains a complex challenge and, up to this date, there is no documentation strictly dedicated to the integration of fMRI to guide dMRI tractography (i.e. bests practices, step-by-step guide, recommendations, etc.). The first objective of this thesis was to provide an integrative synthesis of the methodological aspects related to the integration of fMRI to guide dMRI tractography through a scoping review (article/study #1). Our results are organized in 19 findings which concern the methodological challenges associated with this multimodal combination technique. We there offer recommendations, solutions and identify gaps in the literature.

The second objective of this thesis was to map the brain network involved in picture naming by integrating fMRI to guide dMRI tractography in healthy young adults (article/study #2). By applying the knowledge obtained from article/study #1 in the context of an experimental study, we were able to propose a neurocognitive model of picture naming. In this model, we confirm the presence of a ventral and dorsal information processing pathway. Our results also suggest that the posterior parts of the inferotemporal cortex and superior temporal gyrus may serve as

an interface between these two information processing pathways. This study also supports the hypothesis of an indirect ventral pathway that relays through the anterior temporal lobe.

Finally, this thesis offers a useful tool for researchers who wish to use this multimodal integrative method, advance knowledge or develop new methodological tools. Thanks to the integration of fMRI to guide dMRI tractography and the triangulation of data from other methods, this thesis was able to offer a complex and comprehensive look at the cognitive processes and neurobiological basis involved in picture naming. Again, this is also a very relevant tool for all clinicians who use picture naming in their everyday practice.

Keywords: multimodal imaging, Magnetic resonance imaging, fMRI, tractography, white matter, language, picture naming, scoping review

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Liste des sigles et abréviations

Français :

(PPA) : Aphasie primaire progressive

(AVC): Accident vasculaire cérébraux

(BA #): Aire de Brodmann

(FA): Anisotropie fractionnelle

(BNT): Boston Naming Test

(SD): Déconvolution sphérique

(MD): Diffusivité moyenne

(AF): Faisceau arqué

(emC): Faisceau temporo-frontal de la capsule extrême

(IFOF): Faisceau fronto-occipital inférieur

(ILF): Faisceau longitudinal inférieur

(MdLF): Faisceau longitudinal médian

(SLF): Faisceau longitudinal supérieur

(UF): Faisceau unciné

(DTI): Imagerie par diffusion de tenseur

(IRM): Imagerie par résonance magnétique

(IRMd): Imagerie par résonance magnétique de diffusion

(IRMf): Imagerie par résonance magnétique fonctionnelle

(rs-IRMf): Imagerie par résonance magnétique fonctionnelle à l'état de repos / resting-state

(IRMs): Imagerie par résonance magnétique structurelle

(QBI): Imagerie Q-ball

(LTAs): Lobes temporaux antérieurs

(LTAs): Lobes temporaux antérieurs

(MA): Maladie d'Alzheimer

(NuFO): Nombre d'orientation des fibres

(BOLD): Signal « blood oxygen level-depedant »

(TDQ): Test de dénomination de Québec

(FAT): Tract aslant frontal

(TDSP): Trouble du développement des sons de la parole

(lv-PPA): Variante logopénique de l'aphasie primaire progressive

(nv-PPA): Variante non-fluente/agrammatique de l'aphasie primaire progressive

(STS) : Sillon temporal supérieur

(sv-PPA): Variante sémantique de l'aphasie primaire progressive

Anglais:

(AD): Alzheimer Disease

(ACT): Anatomically Constrained Tractography

(AD): Axial diffusivity

(BNT): Boston Naming Test

(BT): Brain Tumor

(CB): Cingulum bundle

(CSD): constrained spherical deconvolution

(CMC): Continuous Map Criterion

(CST): corticospinal track

(DP): Developmental Prosopagnosia

(DSI): Diffusion Spectrum Imaging

(DTI): Diffusion tensor imaging

(DWI): Diffusion-weighted images

(DEC): Directionally encoded color

(DCM): Dynamic causal modeling

(TE): Echo Time

(EPI): Echo-planar imaging

(FWE): Familly wise error

(FoV): Feild of View

(FOD): Fiber orientation distribution

(FOD): Fiber orientation distribution

(fODF): Fiber orientation distribution function

(5TT): Five-tissue-type segmentation

(FSL): FMRIB Software Library

(FA): Fractional anisotropy

(FWHM): Full width half maximum filter

(FUGa): Fusiform gyrus anterior part

(FUGp): Fusiform gyrus posterior part

(GLM): General linear model

(GRAPPA): GeneRalized Autocalibrating Partial Parallel Acquisition

(GFA): Generalized fractional anisotropy

(GTS): Gilles de la Tourette's Syndrome

(HRF): Hemodynamic response function

(HARDI): High Angular Resolution Diffusion Imaging

(IFGpo): Inferior frontal gyrus pars orbitalis

(pITG): Inferior temporal gyrus posterior part

(jICA): Joint independent component analysis

(LGN): Lateral geniculate nucleus

(LPCA): Local principal component analysis

(lv-PPA): Logopenic variant of the primary progressive aphasia

(MD): Mean diffusivity

(MOG): Middle occipital gyrus

(MCI): Mild cognitive impairment

(MNI): Montréal neurological institute

(MEMPRAGE): Multi Echo Multi Planar Rapid Gradient Echo

(MS): Multiple Sclerosis

(nv-PPA): Non-fluent variant of theprimary progressive aphasia

(OBPP): Obstetric brachial plexus palsy

(ODF): Orientation distribution function

(PVSAT): Paced Visual Serial Addition Test

(PFT): Particle Filtering Tractography

(PNT): Philadelphia Naming Test

(PSA): Post-Stroke Aphasia

(PCG): Precentral gyrus

(pre-SMA): Pre-supplementary motor area

(PIBI): Probability index on forming part of the bundle of interest

(RD): Radial diffusivity

(ROIs): Regions of interest

(TR): Repetrition Time

(SCZ): Schizophrenia

(sv-PPA): Semantic variant of the primary progressive aphasia

(SD): Spherical deconvolution OU Standard deviation

(SD): Standard deviation

(SPM): Statistical Parametric Mapping

(pSTG): Superior temporal gyrus posterior part

(SMA): Supplementary motor area

(SMA): Supplementary motor area

(TLE): Temporal Lobe Epilepsy

(TP): Temporal pole

(TDI): Track density images

(TBSS): Tract-based spatial statistics

(TBI): Traumatic Brain Injury

(VLSM): Voxel-based lesion-symptom mapping

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Chapitre 1 – [Contexte Théorique]

Avis au lecteur : L'utilisation du genre masculin a été adoptée afin de faciliter la lecture et n'a aucune intention discriminatoire.

1. Introduction générale

Si l'approche localisationniste[1] des fonctions cognitives a su acquérir ses lettres de noblesse tout au long des siècles passés, les travaux de recherche scientifique au tournant du 21e siècle auront enfin su démontrer que cette conception théorique, bien que pertinente à plusieurs égards, présente d'importantes lacunes (Catani et Ffytche, 2005; Mesulam, 1990). Les conceptualisations « plus modernes » de l'implémentation physique des fonctions cognitives supportent davantage la proposition qu'elles reposent sur le travail orchestré d'un ensemble de régions cérébrales formant des réseaux spécialisés (Biswal et al., 1995; Damoiseaux et Greicius, 2009; Fox et al., 2005; Seeley et al., 2009).

L'étude des réseaux cérébraux supportant les fonctions cognitives présente néanmoins plusieurs défis. Parmi ceux-ci, on retrouve notamment le fait qu'aucune méthode d'imagerie cérébrale ne permette à elle seule de mesurer la dynamique fonctionnelle du cerveau à la tâche tout en mesurant simultanément ses aspects structurels (ex. composition physique de la matière et/ou connexions axonales) (Huettel et al., 2014; Sui et al., 2014). Pour pallier ce problème, de plus en plus de chercheurs se tournent vers l'imagerie cérébrale multimodale en tentant de combiner les informations acquises afin de répondre à plusieurs questions fondamentales issues des sciences cognitives (Calamante et al., 2013; Damoiseaux et Greicius, 2009; Soares et al., 2013; Zhu et al., 2014).

Cette thèse vise, dans un premier temps, à documenter et effectuer une synthèse intégrative des connaissances/méthodes existantes en ce qui concerne l'intégration de l'imagerie par résonance magnétique fonctionnelle (IRMf) à la tractographie (étude #1).

[1] Courant théorique voulant que des fonctions spécifiques soient tous et chacune localisées au sein de zones spécifiques de l'encéphale.

Dans un deuxième temps, nous appliquerons les connaissances/méthodes issues de l'étude #1 afin de cartographier les réseaux corticaux impliqués dans la dénomination d'images (étude #2). Il s'agira, entre autres, de répertorier l'ensemble des aires corticales mobilisées lors de la dénomination d'images, mais surtout d'étudier l'organisation structurelle de la matière blanche qui permet la communication entre ces différentes régions cérébrales.

Afin d'introduire le premier article proposé pour cette thèse, nous aborderons d'abord l'historique de la transition du schème localisationniste et de la spécialisation fonctionnelle des aires cérébrales vers une approche plus axée sur les réseaux cérébraux. Ensuite, nous discuterons de la pertinence de combiner les méthodes d'imagerie cérébrale et les types de combinaisons existantes. Considérant que la thèse portera surtout sur l'intégration de l'IRMf à la tractographie, nous ferons un bref survol des différentes méthodes d'acquisition et d'analyses de données issues de l'imagerie par résonance magnétique (IRM). Afin d'introduire le second article, nous traiterons d'abord des modèles permettant d'expliquer les mécanismes cognitifs sous-jacents à la dénomination et nous aborderons ensuite ses substrats neuroanatomiques.

2. Bref historique de la localisation cérébrale des fonctions cognitives

La neuropsychologie est une branche des sciences cognitives qui étudie l'impact des lésions cérébrales ou des altérations neurodéveloppementales afin de mieux comprendre le lien entre le système nerveux central et les comportements ou les processus de pensées (Vallar et Caputi, 2020). Il est difficile d'établir avec précision le moment où cette quête intellectuelle aurait officiellement débuté. D'un point de vue historique, nous pouvons remonter jusqu'à l'antiquité et même la préhistoire pour retracer les balbutiements de l'intérêt de l'humain envers ses comportements et le lien qu'ils entretiennent avec le système nerveux central (p.ex. réalisation de trépanation chez des hommes il y a plus de 7000 ans, le papyrus d'Edwin Smith suggérant un lien entre le cerveau et les comportements ≈ - 1500 AV-JC et les écrits d'Hippocrate faisant mention que : « le cerveau n'est pas seulement impliqué dans les sensations, mais est aussi le siège de l'intelligence ») (Alt et al., 1997; Bear et al., 2016; Breasted, 1930). Bon nombre de pionniers ont par la suite contribué à faire avancer notre compréhension du fonctionnement du système nerveux central et de son rôle dans nos processus de pensée/comportements (voir Vallar

and Caputi, 2020 pour une revue historique plus complète et nuancée). Bien qu'il n'y ait pas de date officielle associée à la naissance de la neuropsychologie en tant que discipline scientifique, plusieurs reconnaissent la publication concernant le cas du patient aphasique « Leborgne » par Paul Broca en 1861 comme étant un marqueur significatif du début de l'existence de la neuropsychologie. Autrement, le terme « Neuropsychology » apparaîtra officiellement dans les écrits au début du 20e siècle pour devenir d'usage commun dès la seconde moitié du 20e siècle au tournant de la révolution cognitive (Vallar et Caputi, 2020).

Puisque la neuropsychologie a émergé via l'observation et l'évaluation méticuleuse d'atteintes cognitives ou comportementales spécifiques auprès de patients cérébrolésés, c'est sans surprise que le concept de localisation cérébrale des fonctions cognitives a rapidement émergé. En effet, les racines de la discipline proviennent surtout de la pratique des corrélations anatomo-cliniques issues de la neurologie (c.-à-d. établir un lien entre la localisation d'une lésion cérébrale et un déficit cognitif/comportemental) (Eustache et al., 2013). Si bien qu'avec le temps ses pionniers ont proposé de plus en plus de modèles ou de théories de la pensée basés majoritairement sur des études à cas unique (ou de petits groupes ayant des symptômes et des lésions en commun) qui donneront en définitive le coup d'envoi pour à la quête scientifique de la cartographie cérébrale des fonctions mentales.

2.1 La spécialisation fonctionnelle des régions cérébrales et ses limites

À partir des années 1970 et jusqu'à la fin du 20^{e} siècle, l'essor des méthodes d'investigation, notamment l'avènement des outils d'imagerie cérébrale, permettra d'établir un ancrage scientifique plus solide au courant localisationniste. Une pléthore d'études parviendront à apporter des preuves empiriques validant et raffinant les modèles anatomo-fonctionnels plus contemporains de la cognition humaine. Ces études auront l'avantage de porter sur de plus grands groupes de participants vivants (patients ou individus en santé).

Parmi certains de ces travaux ayant eu une influence considérable, retenons d'abord et avant tout les études de stimulation électrique du cortex cérébral des patients éveillés au cours de neurochirurgies (Penfield et Rasmussen, 1950). Celles-ci ont notamment permis de dresser les célèbres cartes fonctionnelles (homonculus) du cortex moteur (gyrus précentral) et

somesthésique (gyrus postcentral) tout en enracinant davantage l'idée que ces cortex n'ont aucune autre fonction que la motricité et/ou la somesthésie (Gallese et Lakoff, 2005; Pulvermüller, 2012). Dans le même ordre d'idée, plusieurs chercheurs établiront des corrélations anatomocliniques également appuyées par les études en imagerie fonctionnelle chez le sujet en santé (p. ex. le rôle de l'aire V4 au sein du cortex extra strié dans le traitement perceptuel des couleurs/l'agnosie des couleurs (Martin et al., 1995; Simmons et al., 2007; Stasenko et al., 2014; Zeki, 1980) ou l'implication de la jonction temporo-pariéto-occipitale droite dans le déploiement de l'attention visuo-spatiale/le syndrome de l'héminégligence unilatérale (Posner et Raichle, 1994; Vallar et Perani, 1986)). Certains en viendront même à se détacher des étiquettes neuroanatomiques classiques pour proposer de nouvelles étiquettes fonctionnelles à des régions cérébrales exhibant une spécialisation. Pour n'en nommer que quelques-uns, on peut penser aux : « parahippocampal place area » (Aguirre et al., 1998; Bohbot et al., 1998; Epstein et Kanwisher, 1998; Habib et Sirigu, 1987), « extra-striate body area » (Downing et Kanwisher, 2001), « visual word form area » (Cohen et al., 2002; Turkeltaub et al., 2014) et le très célèbre « fusiform face area » particulièrement associé au cas de la prosopagnosie (De Renzi et al., 1994; Kanwisher et al., 1997).

Cette apparente sélectivité des régions cérébrales au traitement de l'information laissait entrevoir un avenir très prometteur aux explorateurs de la cartographie cérébrale des fonctions cognitives chez l'humain! Évidemment, cette quête de compréhension ne s'est pas déroulée de façon aussi linéaire que le présent texte peut le laisser sous-entendre… En fait, différentes écoles de pensées se sont formées et ont coexisté entraînant de vifs débats et laissant place à des idées dominantes à chaque époque (p. ex. équipotentialité, localisationnisme et associationnisme) (voir Catani et al., 2005 pour une revue historique plus détaillée). Toutefois, la rigueur de la méthode scientifique et la créativité des chercheurs ont su fournir suffisamment de preuves pour remettre en question la conception purement localisationniste plutôt rigide et visiblement limitée. Ceci a permis de laisser place à une vision plus nuancée où la spécialisation fonctionnelle des aires cérébrales demeure pertinente, mais devient relativisée par le fait que : **1)** une même région cérébrale peut-être impliquée dans plusieurs fonctions cognitives (problème de la spécificité) et que **2)** généralement plus d'une région cérébrale contribuent de façon significative à une fonction

ou au processus cognitif en étant interconnectées par des fibres de matières blanches qui permettent de transmettre les influx nerveux d'un territoire à l'autre (organisation en réseau plutôt qu'en unité modulaire totalement indépendante). Sans être complètement exhaustive pour aborder le problème de la spécificité, l'étude de Gauthier et al. peut être vu comme une preuve de concept qui remet en question la spécificité du « fusiform face area » dans la reconnaissance des visages. Elle démontre que cette région cérébrale s'active aussi lors de la perception d'objets pour lesquels nous développons une expertise (Gauthier et al., 1999). À ceci s'ajoute le fait que les cortex sensori-moteurs aient un rôle, bien que partiel, à jouer dans la cognition sémantique (Pulvermüller, 2012).

Par ailleurs, de plus en plus d'études permettent de mettre en lumière que les fonctions cognitives sont organisées en réseaux parallèles distribués (Duffau, Herbet, et al., 2013; Mesulam, 1990). Dans cet ordre d'idée, des recherches démontrent que les maladies neurodégénératives telles que la Maladie d'Alzheimer (MA) et/ou la variante sémantique de l'aphasie primaire progressive (sv-PPA) vont « attaquer » préférentiellement des réseaux cérébraux plutôt que de s'en prendre uniquement à des régions focales ou aléatoirement à l'ensemble de l'encéphale (Seeley et al., 2009). Qui plus est, plusieurs chercheurs vont avancer que ces maladies engendrent des syndromes de déconnexion qui provoquent les déficits cognitifs propres à chaque pathologie (Chapleau et al., 2019; Delbeuck et al., 2003; Guo et al., 2013; Montembeault et al., 2016, 2019; Reid et Evans, 2013; Seeley et al., 2009). De façon similaire, bon nombre d'études effectuées auprès de survivants d'accidents vasculaires cérébraux (AVC) vont mettre en évidence la présence d'altérations métaboliques et/ou structurelles distantes du site original de la lésion (Carrera et Tononi, 2014).

Il va sans dire que plusieurs de ces démonstrations ont pu être effectuées grâce au développement des outils et techniques issus de la neuro-imagerie que nous allons maintenant aborder. Pour rester en phase avec les visées de cette thèse et à des fins de concision, nous limiterons cette présentation à l'IRMf et l'IRM de diffusion (IRMd).

3. L'imagerie par résonance magnétique (IRM)

L'IRM est un appareil très polyvalent qui permet d'étudier le système nerveux central in-vivo de façon non invasive selon plusieurs angles d'analyse : fonctionnelle (IRMf), anatomique ou morphologique (IRM structurelle [IRMs]) et il permet également d'étudier l'organisation des fibres de matières blanches ainsi que leurs propriétés microstructurelles (IRM de diffusion [IRMd]). Tel qu'évoqué précédemment, nous aborderons uniquement l'IRMf, l'IRMd et les types de combinaisons multimodales possibles.

3.1 IRMf : Imagerie par résonance magnétique fonctionnelle

Sommairement, l'IRMf est une technique qui permet de mesurer indirectement l'activité cérébrale puisque l'augmentation du taux de décharge neuronale (potentiel d'action) engendre une réponse hémodynamique caractéristique afin de répondre/compenser à la demande métabolique imposée (phénomène du couplage neurovasculaire) (Huettel et al., 2014; Logothetis, 2008). Ainsi, l'IRMf mesure les fluctuations du signal « blood oxygen level-depedant » (BOLD) dans le temps en exploitant le fait que l'hémoglobine réagit différemment aux champs magnétiques en fonction de son couplage ou non à une molécule d'oxygène (Chen et Glover, 2015; Huettel et al., 2014).

Les analyses de contraste basées sur la tâche (voir Task-Based fMRI dans Chen et al., 2015) permettent d'établir un lien fonctionnel entre l'augmentation de l'activité neuronale au sein de régions cérébrales et l'exécution d'une tâche cognitive dans l'appareil IRM lorsque comparée à un « niveau de base[2] » (p.ex. génération de verbe > répéter le mot « bonjour »). En plus des contrastes basés sur la tâche, d'autres types d'analyses peuvent être effectuées à l'aide de l'IRMf en contexte de tâche ou encore en situation de repos (*« resting state »*) telles que les analyses de connectivités fonctionnelles et/ou les analyses de connectivité effective. Bien que ces méthodes soient pertinentes, elles ne seront pas centrales dans le cadre de cette thèse. Nous orientons

[2] Le terme « niveau de base » ici signifie tout point de comparaison pertinent (ex. état de repos, croix de fixation, tâches non reliées, etc.).

donc le lecteur vers les publications de Chen et al., 2015 et/ou Friston, 2011 pour de plus amples détails et références à ce sujet.

3.2. IRMd : Imagerie par résonance magnétique de diffusion

L'IRMd permet quant à elle de sonder les propriétés microstructurelles des tissus cérébraux en mesurant le signal de diffusion des molécules d'eau. Ces dernières ont la propriété de constamment effectuer des déplacements/mouvements dans des directions aléatoires (« Brownian motions ») (Descoteaux et Poupon, 2012; Jones, 2010; Van Hecke et al., 2016). Cependant, dans un milieu où les restrictions structurelles sont plus grandes (p. ex. au sein d'un faisceau de matière blanche contenant de nombreux axones myélinisés alignés sur un même axe), les mouvements des molécules d'eau n'auront d'autres choix que de respecter les contraintes physiques qui leur sont imposées. Par le fait même, elles auront donc tendance à adopter une trajectoire de diffusion similaire à la structure axonale environnante, ce mouvement sera alors qualifié d'anisotropique. À l'inverse, lorsque les contraintes physiques sont nulles ou très faibles, les molécules d'eau adopteront librement des trajectoires aléatoires et, par conséquent, le signal enregistré par l'IRMd sera réduit. Il s'agit donc de mouvements isotropiques, tels qu'observés au sein du liquide céphalo-rachidien des ventricules cérébraux (Descoteaux et Poupon, 2012; Jones, 2010; Van Hecke et al., 2016).

Plusieurs techniques de modélisation ont été proposées afin d'estimer les propriétés microstructurelles des tissus biologiques et chacune d'entre elles possède des avantages et des inconvénients (voir Descoteaux et Poupon, 2012 à ce sujet). Parmi les plus populaires, on retiendra l'imagerie par diffusion de tenseur (DTI) (Basser et al., 1994), l'imagerie Q-ball (QBI) (Tuch, 2004), les modèles à tenseurs multiples (Peled et al., 2006) et la déconvolution sphérique (SD) (Tournier et al., 2004). Ces techniques de modélisation vont permettre d'effectuer des analyses quantitatives concernant les propriétés microstructurelles des tissus (plus traditionnellement au niveau de la matière blanche) selon différentes métriques telles que : l'anisotropie fractionnelle (FA), la diffusivité moyenne (MD) ou encore le nombre d'orientations des fibres (NuFO). Ces analyses peuvent être effectuées selon une approche plus standard basée

sur les voxels ou au niveau de la fibre de matière blanche reconstruite par tractographie (Van Hecke et al., 2016).

En utilisant les données issues de l'IRMd, la tractographie est actuellement la seule méthode qui permet d'étudier l'organisation des fibres de matière blanche in vivo et de façon non invasive. En effet, avant l'avènement de la tractographie, les chercheurs devaient se fier uniquement à des techniques invasives afin d'étudier les fibres de matière blanche. Il s'agissait en outre d'effectuer des études comparatives chez l'animal à l'aide de traceurs radioactifs antérogrades/rétrogrades ou encore de procéder à des dissections post-mortem sur des cadavres humains (Axer, 2011; Chanraud et al., 2010).

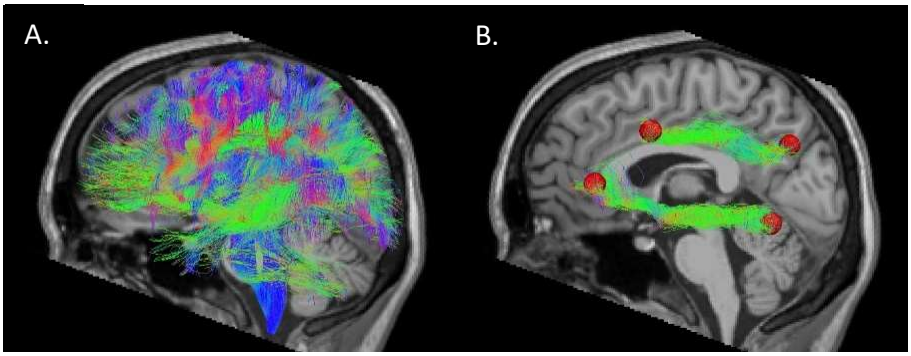
La tractographie correspond à une reconstruction virtuelle des tracts[3] de matière blanche. Certains chercheurs iront même jusqu'à qualifier cette méthode de « dissection in-vivo » (Catani et Thiebaut de Schotten, 2008). La tractographie peut être effectuée en utilisant divers types d'algorithmes tractographiques dont les avantages et inconvénients sont abordés dans les ouvrages suivants : Alexander, 2010; Descoteaux et Poupon, 2012; Maier-Hein et al., 2017; Parker, 2010. Pour ce faire, le chercheur peut effectuer un tractogramme intégral de l'encéphale (traduction libre de « whole-brain tractogram ») et ensuite sélectionner les tracks qui relient les régions cérébrales d'intérêt (Figure 1A). Il est également possible de focaliser le travail computationnel sur une tâche plus circonscrite en effectuant la tractographie uniquement entre des régions cérébrales d'intérêt et en ignorant ainsi le reste de l'encéphale (figure 1B).

Il est important de ne pas confondre cette reconstruction virtuelle de la matière blanche ayant parfois l'apparence de spaghettis (« streamlines » en anglais) avec les projections axonales en soi. En effet, ce type de représentation visuelle peut parfois confondre le lecteur non averti. Qui plus est, bien que ces représentations visuelles tridimensionnelles soient souvent pourvues d'un code de couleurs indiquant l'orientation principale des tracks (ex. fibres de projection en bleu, fibres commissurales en rouge et fibres associatives en vert), la tractographie ne permet en aucun cas

[3]Afin de respecter la nomenclature établie au sein de la littérature scientifique, veuillez noter que le terme « track » sera utilisé dans cet ouvrage pour faire référence aux produits/résultats de la tractographie alors que le terme « tract » sera réservé pour désigner l'entité anatomique (c.-à-d. les faisceaux de matière blanche).

d'inférer la direction des influx nerveux qui y transigent (Descoteaux et Poupon, 2012; Jones, 2010; Van Hecke et al., 2016).

Figure 1. – Exemples de tractographies effectuées à l'aide d'un algorithme probabilistique.



La section **A.** représente un tractogramme intégral de l'encéphale et la section **B.** représente des tractographies circonscrites entre des régions d'intérêt désignées. À noter que les tracks de projection sont identifiés en bleu, les tracks commissuraux en rouge et les tracks associatifs en vert.

Les données issues de la tractographie permettent plusieurs types d'analyses. Elles peuvent d'abord servir sur le plan clinique en permettant d'observer une rupture/déconnexion au sein d'un faisceau de matière blanche ou encore d'assister la neurochirurgie dans le cas de déviations structurales dues à une tumeur (Guye et al., 2003; Kleiser et al., 2010; Niu et al., 2016; Schonberg et al., 2006; Uzuki et al., 2009). La tractographie permet également d'effectuer des analyses qualitatives et quantitatives en ce qui concerne l'organisation topographique des tracts de matières blanches. Il sera précisément question de ce dernier type d'analyse dans le cadre de l'article #2 de cette thèse. Tel que cela fut abordé précédemment, la tractographie rend aussi possible l'analyse quantitative des propriétés microstructurelles (puisque basée sur l'IRMd) au niveau du track. Cette technique nommée tractométrie peut être effectuée sur l'ensemble du track d'intérêt ou à un niveau plus granulaire par profilage tractométrique (traduction libre du terme « tract profiling ») (pour plus de détails, consultez les ouvrages de Cousineau et al., 2016; Yeatman et al., 2012).

3.3. Imagerie multimodale en IRM

Bien qu'une méthode ou technique d'imagerie cérébrale prise individuellement puisse s'avérer suffisante pour venir répondre à certaines questions de recherche, il existe bon nombre de questions qui nécessiteront quant à elles une investigation multimodale pour venir objectiver un

phénomène donné. À cet égard, il y a un intérêt grandissant dans la communauté scientifique pour la combinaison des données multimodales issues de l'IRM (Soares et al., 2013).

Parmi les façons de combiner les modalités IRM, nous nous intéressons particulièrement au cas de l'intégration des données issues de l'IRMf (contrastes basés sur la tâche) pour guider la tractographie. Cet intérêt provient du fait que cette approche permet de dégager des connaissances relatives au réseau cérébral impliqué dans la réalisation d'une tâche spécifique (ex. nommer des images) en plus de permettre l'étude des fibres de matière blanche qui desservent la communication neurale au sein de ce réseau. Une telle connaissance des réseaux fonctionnels et des connexions sous-jacentes est tout à fait pertinente afin de mieux comprendre tant l'implémentation physique des fonctions cognitives, mais aussi les pathologies qui les affectent. Cette approche permet également d'étudier la nature dynamique ou interactive qu'entretiennent les différentes régions cérébrales.

Néanmoins, cette approche multimodale est relativement récente et particulièrement complexe à réaliser. Si certains procéduriers et recommandations méthodologiques basés sur des critères empiriques existent en ce qui concerne l'IRMf, l'IRMd et/ou la tractographie pris individuellement, il n'existe cependant à ce jour aucun document dédié à l'intégration de ces deux modalités. Un examen de la portée (« scoping review » en anglais) pourrait en outre permettre d'éclaircir ce qui a été fait et ce qui peut être amélioré en ce qui concerne précisément l'intégration de l'IRMf pour guider la tractographie. Ce type d'étude se veut une approche systématique qui permet de faire état de l'étendue de la recherche et d'identifier les lacunes en ce qui concerne le développement des connaissances ou la compréhension d'un domaine/sujet donné en vue de proposer des pistes de solutions/investigations pour le futur (Peterson et al., 2017; Pham et al., 2014; Tricco et al., 2016, 2018).

4. La dénomination d'images

En quoi est-ce utile de se pencher sur le cas de la dénomination d'images ou d'objets dans le cadre de cet ouvrage doctoral ? Les arguments sont multiples tant d'un point de vue pragmatique que théorique.

Tout d'abord, on ne peut nier le fait que notre capacité à nommer des objets ou concepts constitue un élément fondamental de notre capacité à communiquer verbalement. Ceci est vrai tant pour le langage oral que les autres formes de langage (ex. écrit ou signé). En ce sens, une perturbation d'origine acquise ou neurodéveloppementale de cette précieuse aptitude peut mener à des limitations au quotidien (ex. diminution de la fluidité, erreurs de types paraphasiques, discours vide de sens, altération des capacités d'élaboration verbale et donc de la difficulté à se faire comprendre par les autres). Conséquemment, ce type d'atteintes langagières peut mener à une diminution de la qualité de vie, de l'isolation, une humeur dépressive et même à un risque accru de suicide (Gall, 2001; Rice, 1993; Worrall et Holland, 2003). Ainsi, il apparait impératif de bien comprendre les mécanismes neurocognitifs derrière nos capacités de dénomination si ce n'est que pour être en mesure de proposer des recommandations, thérapies ou traitements qui permettent de réduire l'impact d'un tel déficit sur le vécu subjectif des individus concernés.

En contexte clinique, la dénomination d'images est l'une des méthodes d'investigation les plus couramment utilisées. Cette méthode permet d'évaluer une multitude de processus cognitifs allant de la perception visuelle jusqu'à la production du mot désiré (ceci sera abordé plus en détail dans la prochaine section) qui, comme nous le savons, sont associés au travail orchestré d'un ensemble de régions cérébrales. Ainsi, ce n'est pas un hasard s'il existe diverses épreuves standardisées qui permettent d'évaluer les capacités de dénomination d'images (ex. Boston Naming Test, Philadelphia Naming test, Expressive One Word Picture Vocabulary Test, Épreuve de dénomination orale d'images DO-80, Test de dénomination de Québec (TDQ-60 et TDQ-30), etc.) (Deloche et Hannequin, 1997; Gardner, 1990; Kaplan et al., 1983; Macoir et al., 2018, 2021; Roach et al., 1996). Ces outils bien connus peuvent être utilisés à des fins d'évaluation diagnostic ou de suivi, mais aussi pour surveiller l'état d'un patient pendant une chirurgie cérébrale éveillée.

Au-delà des enjeux purement pratiques, la science se veut aussi une entreprise intellectuelle qui vise à comprendre les phénomènes naturels, et, parmi ceux-ci figurent la cognition humaine et son implémentation physique dans « l'organe de la pensée » → l'encéphale) (si on accepte, en partie du moins, la position philosophique matérialiste bien entendu). En ce sens, la dénomination d'images se veut également un paradigme utile en psychologie cognitive et en

neurosciences cognitives afin de mieux comprendre l'architecture cognitive et cérébrale qui sous-tend cette aptitude langagière.

4.1. Les bases neurocognitives de la dénomination d'images

Tel que le propose feu Marvin Minsky dans sa célèbre citation « l'esprit[4] est ce que fait le cerveau » (traduction libre de « *The mind is what the brain does* »). En ce sens, il apparait impératif de s'intéresser à l'organisation et au fonctionnement de l'encéphale si l'on désire comprendre la cognition (et vice versa).

Dans cet esprit, nous aborderons les aspects cognitifs de la dénomination et leurs bases neurobiologiques. Pour ce faire, nous présenterons des données issues de diverses méthodes (ex. neuroimagerie, neurostimulation, corrélation anatomoclinique in vivo et études animales) qui nous permettent aujourd'hui d'avoir une lecture scientifique transversale très cohérente. Nous présenterons ensuite un modèle neurocognitif du langage (modèle à deux voies du langage de (Hickok et Poeppel, 2004)) sur lequel se baseront nos travaux de recherche à l'origine de l'article #2 qui propose un modèle intégratif des aspects cognitifs et neuroanatomiques de la dénomination.

4.1.1 Processus cognitifs et corrélats cérébraux de la dénomination

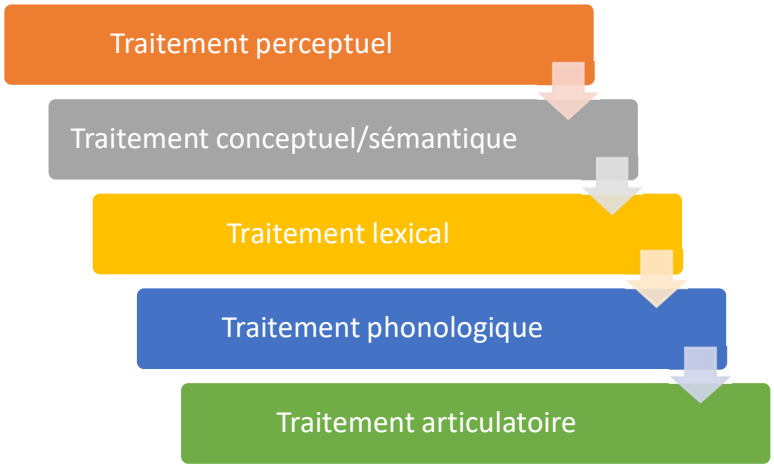
Notre capacité à nommer des images repose sur le travail orchestré d'un ensemble de régions cérébrales bilatérales. Cependant, il est important de préciser que l'hémisphère gauche est dominant pour les aspects langagiers chez la plupart des individus (Dym et al., 2011; Gazzaniga et Sperry, 1967; Ojemann et al., 1989; Posner et Raichle, 1994; Wada et al., 1975). Une des grandes qualités des épreuves de dénomination d'images réside dans le fait qu'elles sollicitent une large étendue de fonctions cognitives et de régions cérébrales malgré l'apparence simple qu'elles peuvent prendre. En contrepartie, ceci peut aussi être perçu comme une grande faiblesse dans la mesure où un rendement moindre à ce type d'épreuve peut s'avérer difficile à interpréter pour l'évaluateur/utilisateur non averti. Malgré ceci, le clinicien expérimenté saura en dégager la signification profonde à travers l'analyse qualitative des comportements ou des erreurs

[4] Ici le mot esprit est utilisé au sens de la pensée humaine et non au sens biblique du terme.

effectuées par l'individu évalué durant sa passation. Par exemple, des erreurs de nature visuelle peuvent témoigner de difficultés sur le plan perceptuel, des délais d'évocation peuvent signifier des troubles d'accès lexical, des erreurs catégorielles peuvent évoquer des atteintes de la sémantique et finalement des difficultés de prononciation peuvent indiquer des atteintes de la forme phonologique ou sur le plan des praxies bucco-faciales. Ces exemples nous permettent déjà d'entrevoir la richesse du traitement de l'information qui réside dans le fait de nommer des images.

Depuis un bon moment déjà, un certain consensus scientifique semble émerger en ce qui concerne les principales étapes du traitement de l'information à l'origine de nos capacités de production orale (dont la dénomination fait partie intégrante) (Caramazza, 1997; Dell, 1986; Dell et al., 1997; Indefrey et Levelt, 2004). Ces étapes concernent 1) le traitement perceptuel, 2) le traitement conceptuel/sémantique, 3) le traitement lexical, 4) le traitement phonologique et 5) le traitement articulatoire. Mentionnons tout de même que des questionnements persistent dans la communauté scientifique à savoir si ces étapes se déroulent selon un mode de traitement séquentiel, parallèle ou interactif (Dell et al., 1997; Indefrey et Levelt, 2004; Levelt, 1999; Levelt et al., 1999; Rapp et Goldrick, 2006).

Figure 2. – Représentation schématique simplifiée des étapes du traitement de l'information sous-jacent la dénomination d'images



Rappel : le schéma présente des processus séquentiels afin de simplifier l'information, bien que cette idée ne soit pas consensuelle telle qu'évoquée dans le texte.

Évidemment, le traitement de l'information lié à la dénomination d'images se doit de débuter au niveau perceptuel puisque l'entrée de l'information se fait via la modalité visuelle. Cette étape englobe le décodage des caractéristiques visuelles élémentaires (ex. contrastes, contours, formes, couleurs, etc.), l'organisation perceptuelle (ex. ségrégation figure/fond, groupement, distance, etc.), la création d'un percept indépendant du point de vue et ultimement la reconnaissance de l'information visuelle présentée (ex. les gnosies). Les régions cérébrales communément associées à ces sous-étapes de traitement de l'information concernent majoritairement les lobes occipitaux ainsi que les régions inférotemporales postérieures bilatéralement (Grill-spector et al., 2001; Haxby et al., 1991; Hubel et Wiesel, 2004; Mishkin et al., 1983; Tootell et al., 1982; Zeki, 1980). Une perturbation ou lésion à ce niveau peut ainsi empêcher la dénomination d'images conséquemment à une défaillance perceptuelle (c'est-à-dire sans atteinte langagière à proprement dire) comme on l'observe souvent dans le cas des agnosies visuelles aperceptives (Humphreys et Riddoch, 1987; Kemmerer, 2014; Mendez et al., 2002; Mizuno et al., 1996; Price et al., 2005).

Le traitement sémantique permet d'associer le percept visuel correctement formé aux connaissances qui le concernent. Ces connaissances sont souvent multiples et stockées dans divers compartiments mnésiques qui peuvent se décliner en moyeux et rayons (« *hub and spoke* ») selon la terminologie de Patterson et al., 2007 dans leur proposition d'un modèle intégratif de la mémoire sémantique. Les rayons concernent les savoirs concrets de plus bas niveau et davantage basés sur l'expérience sensori-motrice (ex. savoir que l'aubergine est mauve ou reconnaître le lion par son rugissement). Ces derniers seraient davantage localisés au sein de régions sensori-motrices (ex. les cortex somesthésiques, moteurs, olfactifs, visuels, etc.) (Kemmerer, 2014; Patterson et al., 2007; Pulvermüller, 2012). Ainsi des perturbations au niveau des rayons (*spokes)* devraient engendrer différentes formes d'agnosie associatives spécifiques (ex. agnosie visuelle associative, agnosie des couleurs, agnosie tactile, etc.) (Gerstmann, 1918; Gertsmann et Benke, 2001; Humphreys et Riddoch, 1987; Patterson et Lambon Ralph, 2016; Pulvermüller, 2012; Simmons et al., 2007; Stasenko et al., 2014). Tandis que les moyeux seraient les engrammes des connaissances transmodales de plus haut niveau (ex. attributs fonctionnels, abstraction et catégorisation) et seraient associés aux lobes temporaux antérieurs (LTAs)

(Damasio et al., 1996; Patterson et al., 2007; Visser et al., 2009). De surcroit, une atteinte des moyeux provoquerait des atteintes sémantiques généralisées et transmodales comme dans le cas de la variante sémantique de l'aphasie primaire progressive (sv-PPA) ou certaines formes d'encéphalites herpétiques (Gorno-Tempini et al., 2011; Hoffman et Lambon Ralph, 2011; Kemmerer, 2014; Patterson et al., 2007; Patterson et Lambon Ralph, 2016; Semenza et Bisiacchi, 1996; Warrington et Shallice, 1984).

Le traitement lexical consiste quant à lui à récupérer les mots candidats associés au concept recherché et de sélectionner, parmi toutes les options soulevées, celui qui correspond le mieux à la requête initiale. Une altération du traitement lexical se manifestera par des difficultés d'accès aux mots tels que des délais d'évocation, des circonlocutions[5] et des paraphasies sémantiques[6]. Ces difficultés peuvent d'ailleurs être observées chez les individus atteints de la variante logopénique de l'aphasie primaire progressive (lv-PPA), d'aphasie de conduction ou d'aphasie anomique (Caplan, 1987; Goodglass et al., 1976; Gorno-Tempini et al., 2008; Kemmerer, 2014). Dans ce cas-ci, il semblerait que plusieurs régions cérébrales de l'hémisphère gauche telles que le gyrus temporal moyen et supérieur, le gyrus frontal inférieur et le lobule pariétal inférieur (c.-à-d. gyrus angulaire) soient impliquées dans le traitement lexical (Badre et Wagner, 2007; Gorno-Tempini et al., 2008; Hickok et Poeppel, 2000; Indefrey et Levelt, 2004; Poeppel et Hickok, 2004). Cependant, tenter d'associer une région spécifique à ce processus versus une autre peut être sujet à controverse pour des raisons méthodologiques et considérant que l'origine de la requête mentale semble avoir une incidence sur les régions qui seront sollicitées (ex. selon une base conceptuelle, lexicale, phonologique ou visuelle) (Badre et Wagner, 2007; Gorno-Tempini et al., 2008; Indefrey et Levelt, 2004).

Le traitement phonologique comprend la récupération des sons qui composent les mots (phonèmes) ainsi que les processus de segmentation et syllabification. Des perturbations de la

[5] Façon d'exprimer sa pensée d'une façon indirecte comme lorsqu'on décrit l'objet ou sa fonction plutôt que de le nommer.

[6] La paraphasie est un type d'erreurs de langage où le locuteur évoque le mauvais mot cible. Dans le cas des paraphasies phonologiques, il s'agit de mentionner un mot composé de sons similaires au mot cible (ex. dire « broue » pour trou ou encore « peigne » pour beigne). La paraphasie sémantique consiste à nommer un mot conceptuellement proche du mot cible (ex. dire « avion » pour hélicoptère ou encore « chien » pour chat).

forme phonologique peuvent donner lieu à des erreurs de production au niveau de la structuration temporelle des sons dans les mots (dont les paraphasies phonologiques font partie). Un individu éprouvant des difficultés à ce niveau pourra par exemple dire ékoile pour étoile, toleil pour soleil ou encore Rean-Jené pour Jean-René. Il est également possible d'observer des conduites d'approche où l'individu tente de s'y prendre à plusieurs reprises pour produire le mot désiré tout en s'autocorrigeant successivement (ex. « le pe… le pa… le pan … le pompier »). Ces difficultés sont souvent manifestes dans le trouble du développement des sons de la parole (TDSP), l'aphasie de conduction ou l'aphasie de Wernicke et la variante non-fluente/agrammatique de l'aphasie primaire progressive (nv-PPA) (Dodd, 2014; Gorno-Tempini et al., 2011; Kemmerer, 2014). Les régions cérébrales de l'hémisphère gauche associées au traitement phonologique englobent surtout les parties postérieures du gyrus temporal supérieur ou moyen alors que les processus de segmentation, de syllabification et prosodification semblent davantage être l'œuvre du cortex préfrontal ventrolatéral (nommément les aires de Brodman 44, 45 et 47) (Corina et al., 2010; Hickok et Poeppel, 2004; Indefrey et Levelt, 2004).

Finalement, une fois la forme sonore du mot bien récupérée, le traitement articulatoire permet de planifier et exécuter la séquence motrice nécessaire qui garantira la production verbale finale. Des difficultés survenant à cette étape empêcheront une élocution adéquate et donc réduira l'intelligibilité du discours comme c'est souvent le cas dans la nv-PPA, l'aphasie de Broca, l'apraxie de la parole et le TDSP (Caplan, 1987; Dodd, 2014; Gorno-Tempini et al., 2011; Kemmerer, 2014; McNeil et al., 1997). Les aires cérébrales reconnues comme étant liés au traitement articulatoire sont le cortex prémoteur (BA 6), le cortex moteur primaire (BA 4), l'aire motrice supplémentaire (BA 6), le thalamus, les ganglions de la base (caudé et putamen) et certaines sous-régions du cervelet bilatéralement (Corina et al., 2010; Guenther, 2006; Guenther et Hickok, 2016; Indefrey et Levelt, 2004).

En somme, une atteinte à une ou plusieurs de ces étapes du traitement de l'information aura nécessairement un impact relativement caractéristique sur notre capacité à nommer des images.

4.2. Les fibres de matière blanche

Dans cette section, nous présenterons sommairement les connaissances qui concernent les principaux faisceaux/tracts intrahémisphériques associés directement ou indirectement à la dénomination. Tel que cela a été précédemment introduit, les fibres de matières blanches permettent de transmettre les influx nerveux d'une région à l'autre au sein d'un même réseau cérébral. Elles sont essentiellement composées d'axones suivant des trajectoires communes. Ces axones sont myélinisés, dans la plupart des cas, par des oligodendrocytes qui leur confèrent une couleur blanchâtre (Bear et al., 2016; Descoteaux et Poupon, 2012).

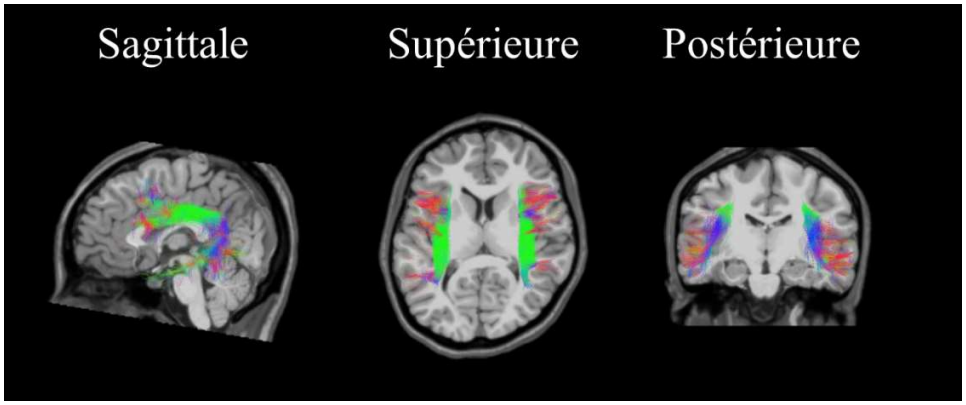
Nous aborderons le faisceau arqué (FA), les différentes branches du faisceau longitudinal supérieur (SLF I, SLF-II et SLF-III), le faisceau longitudinal inférieur (ILF), le faisceau longitudinal médian (MDLF), le faisceau fronto-occipital inférieur (IFOF), le faisceau unciné (UF), le tract aslant frontal (FAT) et le faisceau temporo-frontal de la capsule extrême (emC). Avant de poursuivre, le lecteur doit savoir qu'il s'agit d'un champ de connaissances en plein développement et qui comporte son lot de controverses inhérentes aux limites des différentes méthodologies d'acquisition des données.

4.2.1. Le faisceau arqué (AF)

Lorsqu'il est question de langage, il apparait impératif de débuter la présentation par le faisceau arqué (FA) puisque des décennies durant, le focus scientifique était dédié presque exclusivement à ce faisceau. Cela étant possiblement due au fait qu'il détient une notoriété historique dans ce domaine grâce au modèle neurocognitif classique de Wernicke-Lichtheim-Geschwind. Ce modèle prévoyait en outre que l'AF servait d'unique trajectoire directe entre les aires de Broca et Wernicke (Dick et Tremblay, 2012; Geschwind, 1965; Lichtheim, 1885; Tremblay et Dick, 2016; Wernicke, 1874).

Ce faisceau relie le gyrus temporal supérieur, la partie postérieure du gyrus temporal moyen et une certaine fraction de la jonction occipito-temporale au cortex préfrontal ventrolatéral (BA 47, 45 et 44) ainsi que le cortex prémoteur (c.-à-d. partie ventrale de BA 6) (Axer et al., 2013; Burdach, 1822; Catani et al., 2005; Dejerine, 1895; Geschwind, 1965; Makris et al., 2005; Petrides, 2013; Reil, 1809).

Figure 3. – Représentations tractographiques du faisceau arqué



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L'AF est dominant dans l'hémisphère gauche (Catani et al., 2007; Catani et Thiebaut de Schotten, 2008) et il apparait être relié au traitement phonologique. En effet, il a été reconnu comme étant associé aux troubles qui affectent la capacité de répéter et occasionnent des paraphasies phonologiques (c.-à.-d. l'aphasie de conduction et la lv-PPA) (Caplan, 1987; Galantucci et al., 2011; Geschwind, 1965; Goodglass et al., 1976; Gorno-Tempini et al., 2008; Kemmerer, 2014). Relevons également que la stimulation électrique directe de l'AF gauche engendre des paraphasies phonologiques en contexte de dénomination (Duffau, Moritz-Gasser, et al., 2013; Sarubbo et al., 2015).

4.2.2. Les faisceaux longitudinaux supérieurs (SLF-I, SLF-II et SLF-III)

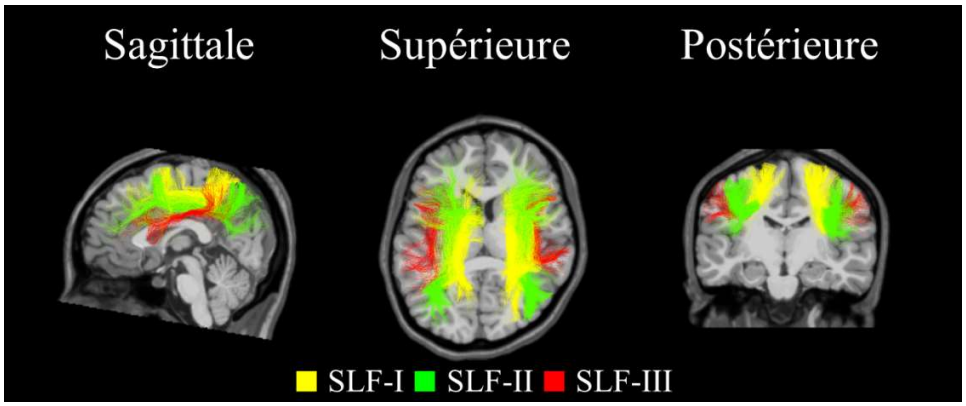
Selon les données de Makris et al., 2005, tous les SLF exhiberaient une latéralisation vers l'hémisphère gauche. Cependant, les auteurs nous mettent en garde quant à la portée de ses résultats obtenus sur leur petit échantillon. De leurs côtés, De Schotten et al., 2011 arrivent à la conclusion que le SLF-I serait plutôt symétrique dans les deux hémisphères.

Le SLF-III[7] émerge de la partie antérieure du lobe pariétal inférieur et atteint le cortex pré-moteur ventral et le gyrus frontal inférieur dont fait partie la pars triangularis du cortex préfrontal ventrolatéral (voir figure 4) (Catani et de Schotten, 2012; Frey et al., 2008; Makris et al., 2005; Petrides, 2013; Schmahmann et Pandya, 2006d).

[7] Parfois décrit comme le segment antérieur indirect selon la nomenclature de (Catani et al., 2005)

Les données issues des études en IRM et en stimulation électrique directe suggèrent que le SLF-III gauche pourraient être impliqué dans les processus articulatoires et/ou la mémoire de travail phonologique (voir Duffau et al., 2003; Galantucci et al., 2011; Maldonado, Moritz-Gasser et Duffau, 2011; Maldonado, Moritz-Gasser, De Champfleur, et al., 2011; Sarubbo et al., 2015; Saur et al., 2008 pour plus de détails).

Figure 4. – Représentations tractographiques des faisceaux longitudinaux supérieurs



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Le SLF-II relie la partie caudale du lobule pariétal inférieur (gyrus angulaire) et la jonction pariéto-occipitale au cortex préfrontal ventrolatéral et dorsolatéral (voir figure 4) (Makris et al., 2005; Petrides, 2013; Schmahmann et Pandya, 2006d).

Tout porte à croire que des lésions au SLF-II gauche pourrait contribuer, en partie du moins, à la symptomatologie de la lv-PPA et la nv-PPA en vertu du fait que ces deux maladies vont causer des atrophies caractéristiques respectivement au niveau du gyrus angulaire et du cortex préfrontal ventrolatéral dans l'hémisphère dominant (Gorno-Tempini et al., 2004). De façon concordante, Galantucci et al., 2011 relèvent des changements microstructurels significatifs au SLF-II gauche dans ces deux pathologies.

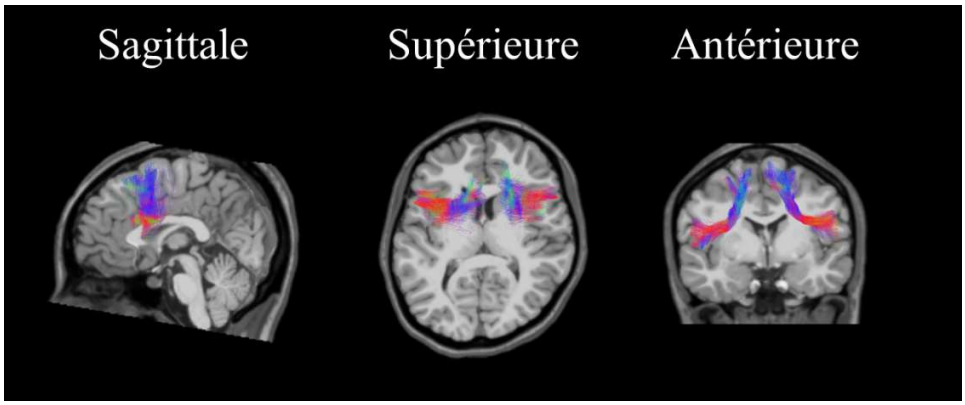
Le SLF-I joint le lobe pariétal supérieur aux le gyrus frontal moyen et l'aire motrice supplémentaire (voir figure 4) (Makris et al., 2005; Petrides, 2013; Schmahmann et Pandya, 2006d). À ce jour, l'implication du SLF-I dans les processus langagiers à proprement dire demeure à être formellement établi. Dans une perspective plus large, nous savons que ce faisceau est associé à la régulation des actions motrices plus complexes qui nécessite de tenir compte du

positionnement relatif des parties du corps, l'intégration visuo-motrice et l'orientation de l'attention visuospatiale (Catani et de Schotten, 2012; De Schotten et al., 2011; Makris et al., 2005; Petrides et Pandya, 2002).

4.2.3. Le tract aslant frontal (FAT)

Le FAT consiste essentiellement en un ensemble de fibres ascendantes relativement courtes qui permettent de connecter le SMA et le pre-SMA au cortex préfrontal ventrolatéral (pars opercularis, triangularis et orbitalis) ainsi que l'insula (Dick et al., 2019; La Corte et al., 2021) (voir figure 5).

Figure 5. – Représentations tractographiques de l'aslant frontal



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De plus en plus de données convergentes semblent indiquer que le FAT gauche serait fonctionnellement impliqué dans l'initiation de la parole, du langage (accès lexical et traitement grammatical) alors que le FAT droit serait plutôt associé aux fonctions exécutives (plus spécifiquement l'inhibition) (voir Dick et al., 2019 ainsi que La Corte et al., 2021 pour des revues).

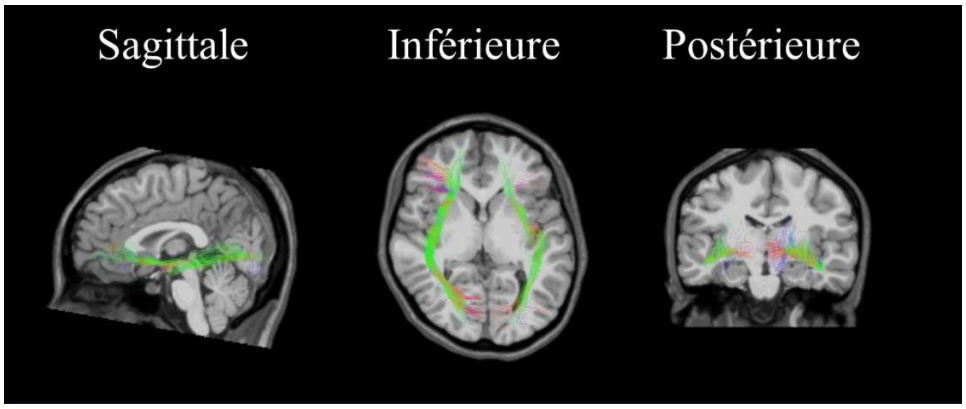
4.2.4. Le faisceau fronto-occipital inférieur (IFOF)

À partir du lobe occipital, l'IFOF longe la partie supérieure du lobe temporal pour atteindre le cortex orbitofrontal ainsi que le gyrus frontal inférieur (voir figure 6) (Catani et Thiebaut de Schotten, 2008; Curran, 1909; Fernández-Miranda et al., 2008; Martino et al., 2010; Petrides, 2013).

Il apparait assez clair que l'IFOF gauche est impliqué dans le traitement sémantique puisque bon nombre d'études en stimulation électrique directe peropératoire démontrent que sa stimulation

engendre presque invariablement des paraphasies sémantiques en contexte de dénomination d'images (De Witt Hamer et al., 2011; Duffau, Moritz-Gasser, et al., 2013; Sarubbo et al., 2015) . D'autres données démontrent que la stimulation de l'IFOF gauche ou droit peut, dans les deux cas, occasionner une incapacité à effectuer des appariements sémantiques d'images (c.-à.-d. Pyramid and Palm Tree Test), ce qui est concordant avec l'hypothèse d'un réseau sémantique bilatéral (Duffau, Moritz-Gasser, et al., 2013; Herbet et al., 2017; Lambon Ralph et al., 2016).

Figure 6. – Représentations tractographiques du faisceau fronto-occipital inférieur

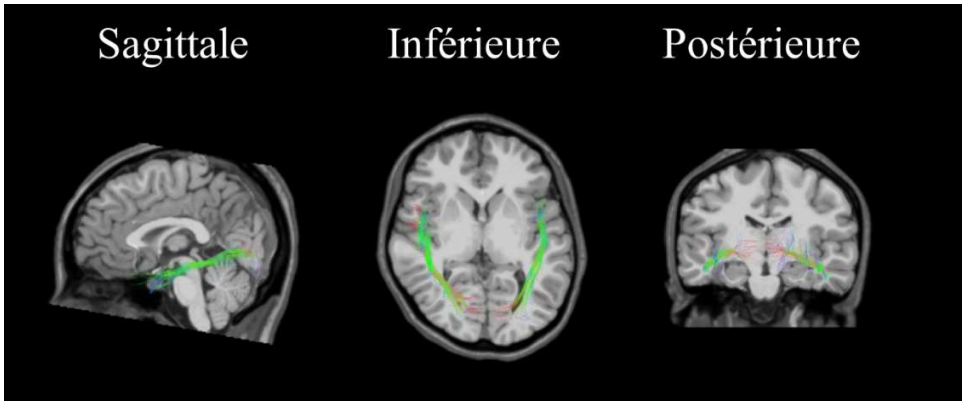


Issues des données du projet re recherche à l'origine de l'article#2

4.2.5. Le faisceau longitudinal inférieur (ILF)

L'ILF est un faisceau associatif qui relie le lobe occipital aux différentes parties du lobe temporal ventral (voir figure 7) (Axer et al., 2013; Burdach, 1822; Catani et de Schotten, 2012; Reil, 1809; Schmahmann et Pandya, 2006b).

Figure 7. – Représentations tractographiques du faisceau longitudinal inférieur



Issues des données du projet re recherche à l'origine de l'article#2

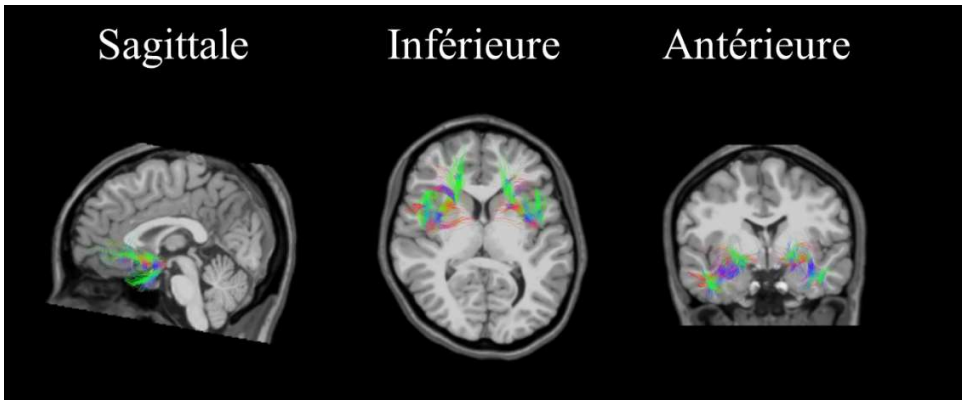
D’un point de vue fonctionnel, l’implication de l’ILF dans la dénomination d’images suscite la controverse puisqu’on relève des données contradictoires à son sujet (voir Agosta et al., 2010; Duffau et al., 2009; Galantucci et al., 2011; Mandonnet et al., 2007; Shinoura et al., 2010). Ce point sera élaboré davantage ci-bas lors de la présentation du faisceau unciné.

4.2.6. Le faisceau unciné (UF)

L’UF permet de relier le lobe temporal antérieur, le gyrus parahippocampique et l’amygdale avec le cortex orbitofrontal ainsi que le cortex préfrontal pars orbitalis en passant entre le claustrum et l’insula (voir figure 8) (Axer et al., 2013; Catani et de Schotten, 2012; Fernández-Miranda et al., 2008; Makris et Pandya, 2009; Reil, 1809; Schmahmann et Pandya, 2006e).

Tout comme l’ILF, la contribution de l’UF à la dénomination d’images est sujette à controverse étant donnée la présence de données contradictoires. En bref, la stimulation électrique directe de l’ILF ou de l’UF gauche ne semble pas compromettre les capacités de dénomination (Duffau , Gatignol, Moritz-Gasser, & Mandonnet, 2009; Mandonnet et al., 2007) alors qu’on relève des altérations microstructurelles de l’ILF et l’UF bilatéralement chez des groupes de patients atteints de la sv-PPA (Agosta et al., 2010; Galantucci et al., 2011). Il serait donc plausible de croire que l’ILF et l’UF puissent agir conjointement à titre de voie secondaire dans le traitement sémantique (Mandonnet et al., 2007; Vigneau et al., 2006).

Figure 8. – Représentations tractographiques du faisceau unciné



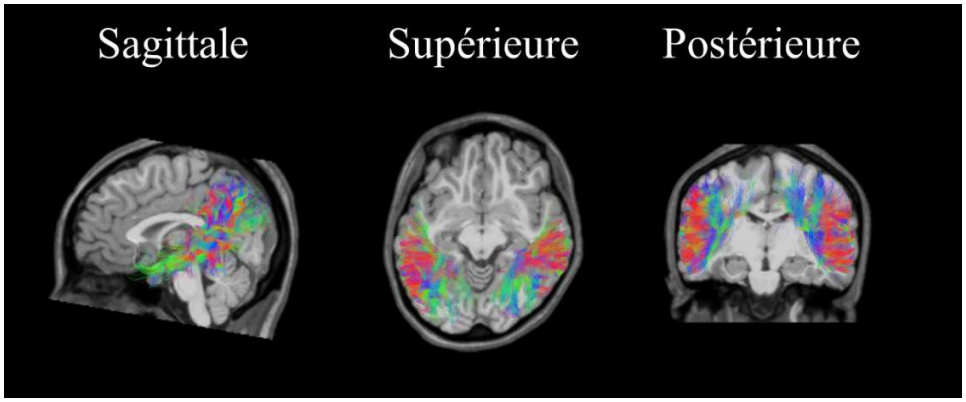
Issues des données du projet re recherche à l’origine de l’article#2

4.2.7. Le faisceau longitudinal médian (MdLF)

Le MdLF relie les lobules pariétaux inférieurs et supérieurs au gyrus temporal supérieur ainsi qu'au pôle temporal (voir figure 9) (Axer et al., 2013; Makris et al., 2009, 2013; Schmahmann et Pandya, 2006c; Seltzer et Pandya, 1984).

Il est possible que le MdLF gauche ait un rôle à jouer dans le traitement lexical puisque Sarubbo et al., 2015 rapportent des cas d'anomie pure en contexte de dénomination d'images lorsqu'une stimulation électrique directe est appliquée dans la partie postérieure gauche de ce qui correspond au MdLF. Cependant, il existe également des données qui viennent remettre en doute cette hypothèse (voir De Witt Hamer et al., 2011; Turken and Dronkers, 2011 pour plus de détails).

Figure 9. – Représentations tractographiques du faisceau longitudinal médian



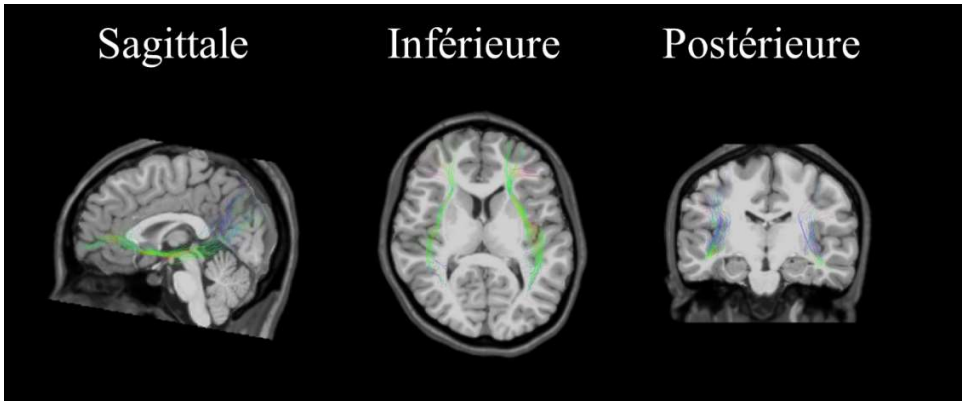
Issues des données du projet re recherche à l'origine de l'article#2

4.2.8. Le faisceau temporo-frontal de la capsule extrême (emC)

Ce faisceau temporo-frontal (voir figure 10) connecte le gyrus temporal supérieur et le gyrus angulaire au gyrus frontal inférieur (aires de Brodman 44, 45 et 47) (Axer et al., 2013; Frey et al., 2008; Makris et Pandya, 2009; Petrides, 2013; Petrides et Pandya, 1988; Schmahmann et Pandya, 2006a).

La contribution de l'emC à la dénomination d'images demeure à être formellement établie. Toutefois, ce faisceau semble davantage être impliqué dans les aspects du traitement sémantique du langage tel que suggéré par Saur et al., 2008 qui démontrent qu'il relie des aires cérébrales de l'hémisphère gauche actives durant la compréhension de phrases.

Figure 10. – Représentations tractographiques du faisceau temporo-frontal de la capsule extrême



Issues des données du projet re recherche à l'origine de l'article#2

4.3. Le modèle à deux voies du langage; un cadre neurocognitif intégratif

En prenant comme point de départ le modèle neurocognitif classique de Wernicke-Lichtheim-Geschwind (Geschwind, 1965; Lichtheim, 1885; Wernicke, 1874), Hickok et Poeppel (2004) ont proposé un cadre neurocognitif qui visait à mieux expliquer la perception de la parole / « *speech perception* » (voir figure 11.).

Ce modèle analogue au fameux paradigme du « où/comment » et du « quoi » en science de la vision (« *what and where/how pathways* ») prévoit deux grandes voies du traitement de l'information (la voie dorsale et ventrale) qui sont dissociables tant sur le plan cognitif qu'anatomique.

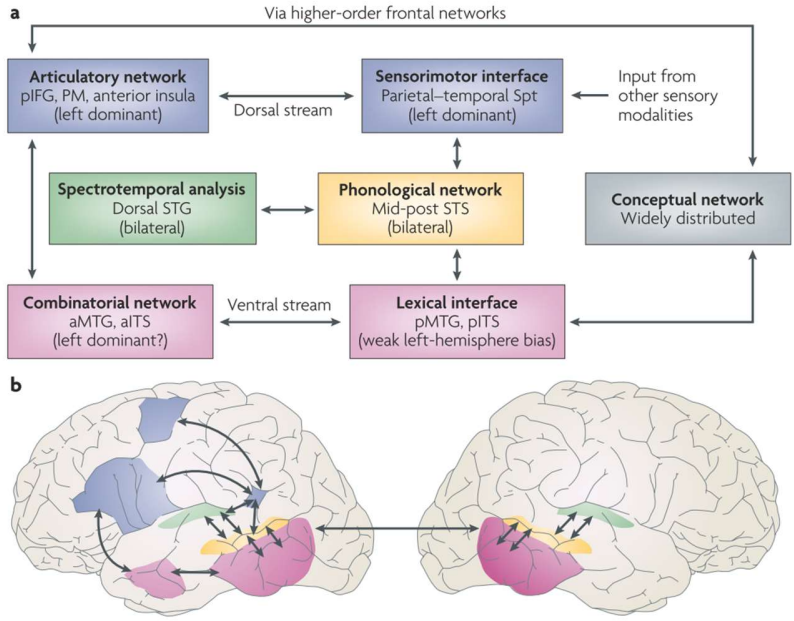
D'une part, la voie dorsale concerne les structures anatomiques davantage localisées dans la partie supérieure de l'encéphale dont les échanges d'information sont garantis par l'AF, les SLFs et le FAT. Cette voie permet « d'associer les sons à la parole » (traduction libre de « mapping sound to speech »). D'une autre part, la voie ventrale concerne plutôt les structures anatomiques davantage localisées dans la partie inférieure de l'encéphale qui sont interconnectées par l'ILF, l'UF, l'IFOF', le MdLF et l'emC. Cette voie ventrale permet « d'associer les sons au sens » (traduction libre de « mapping sound to meaning»).

De façon cohérente avec les informations présentées dans les sections 4.1. et 4.2 de cette thèse, le modèle à deux voies du langage stipule que la voie dorsale serait dominante dans l'hémisphère

gauche alors que la voie ventrale exhiberait un patron davantage bilatéral (Chang et al., 2015; Poeppel et Hickok, 2004; Weiller et al., 2016).

Les dernières révisions de ce cadre théorique (Hickok, 2022) répondent à certaines critiques (ex. la place de la syntaxe dans ce modèle) et on y aborde également l'idée de l'adapter à l'expression volontaire par le langage. On y propose notamment que les tâches expressives (telle que la dénomination d'images) devraient globalement solliciter le même réseau neurocognitif, mais que seul le point d'entrée de l'information et la séquence du traitement devrait varier (donc possiblement plus séquentiel que parallèle en contexte de dénomination selon l'auteur).

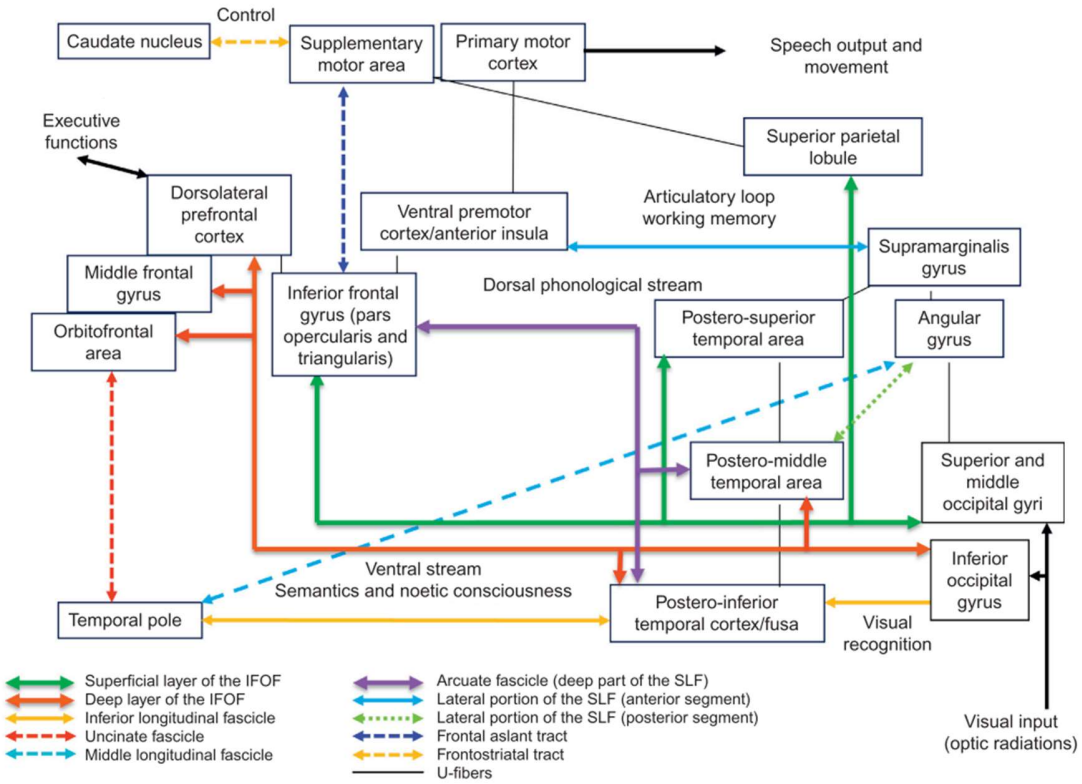
Figure 11. – Représentation schématique du modèle à deux voies du langage



Reproduit de Nature Reviews Neurosciences, vol. 8, Hickok et Poeppel, The cortical organization of speech understanding, page 395, copyright 2007, avec la permission de Nature (licence 1304915).

Cette idée que le modèle à deux voies de la perception de la parole puisse également s'appliquer au langage expressif semble néanmoins solliciter l'intérêt depuis un certain moment dans la communauté scientifique (Chang et al., 2015; Duffau, 2016; Duffau, Moritz-Gasser, et al., 2013) . À cet égard, Duffau et al., 2013 ont proposé un modèle dynamique et hodotopique de la dénomination d'images basé sur les résultats d'études de stimulation électrique directe du cortex et de la matière blanche (voir figure 12).

Figure 12. – Représentation schématique du modèle dynamique et hodotopique de la dénomination d'images (mise à jour de Duffau 2016)



Ce dernier modèle qui incorpore les notions issues du modèle à deux voies du langage permet donc d'expliquer différents phénomènes relatifs à la dénomination d'images (ex. types d'erreurs produites tout en offrant l'avantage de tenir compte simultanément de la matière grise (cortex et noyaux centraux) et blanche (faisceaux/fibres)

5. Objectifs et hypothèses

De façon générale, cette thèse vise à effectuer une synthèse intégrative des aspects méthodologiques associés l'intégration de l'IRMf pour guider la tractographie (article #1). Dans un second lieu, nous désirons à cartographier le réseau cérébral impliqué dans la dénomination d'images chez des jeunes adultes en santé en intégrant l'IRMf pour guider la tractographie (article #2).

5.1. Article #1 étude de la portée **(publié en décembre 2021)**

Considérant qu'il n'existe aucune documentation strictement dédiée à l'intégration de l'IRMf pour guider la tractographie (ex. procédurier, bonnes pratiques, etc.). L'objectif du premier article sera d'effectuer une étude de la portée afin de répertorier toutes les études qui ont intégré l'IRMf (analyses de contraste basées sur la tâche) pour guider la tractographie pour en faire une analyse systématique qualitative et quantitative. Cette analyse permettra d'identifier les défis associés à ce type de combinaison multimodale, de proposer des pistes de solutions et de stimuler la recherche. Il s'agit essentiellement d'un projet de recherche exploratoire qui répond à un impératif pragmatique; notre intention de mener un projet de recherche impliquant l'intégration de l'IRMf pour guider la tractographie en appliquant des méthodes à jours, optimales et scientifiquement valides.

5.2. Article #2 étude empirique **(publié en juin 2022)**

Le second article a pour objectif de cartographier le réseau fonctionnel (IRMf) associé à la dénomination d'images chez l'adulte pour ensuite dévoiler le réseau structurel intra-hémisphérique (tractographie) sous-jacent. Nous émettons l'hypothèse que la tâche de dénomination activera des régions cérébrales classiquement associées à la voie ventrale et dorsale qui seront elles-mêmes interconnectées par des tracts ventraux et dorsaux.

Plus spécifiquement, des activations ventrales sont attendues au niveau du lobe occipital, lobe temporal postérieur et antérieur et le cortex préfrontal ventrolatéral qui seront interconnectés par les voies directes (IFOF et emC) et indirectes (ILF, UF et MdLF). Du côté de la voie dorsale, nous nous attendons à des activations du lobe temporal postérieur, du lobule pariétal inférieur, du cortex préfrontal ventrolatéral et moteur qui seront desservies par l'AF, le SLF-III et le FAT.

Nous émettons aussi l'hypothèse qu'en contexte de dénomination d'images (input visuel) le cortex inférotemporal puisse servir d'interface entre les deux voies du traitement de l'information. Au même titre le lobe temporal supérieur semble jouer un rôle actif dans les deux voies lors de la perception de la parole (Poeppel et Hickok, 2004).

Chapitre 2 – Méthodologie et résultats

Article #1: 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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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 et Adali, 2009; Sui et al., 2014b). 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 bonify our understanding of many brain phenomena (i.e., development, cognition, pathological processes, and psychiatric disorders) (Sui et al., 2014b).

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 et al., 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 et 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 et al., 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, 2010b). 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 et Cercignani, 2010; S. M. 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 et al., 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 et 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, 2010b). 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, 2010a; 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 et Adali, 2009; Sui et al., 2014b) 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 et Adali, 2009; Sui et al., 2014b) (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., 2014b) (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 et al., 2012). Note that this precision will depend upon the implementation 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 et al., 2005; Mesulam, 1990; Sui et al., 2014b). 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 et al., 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 be 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 (D. H. 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 et al., 2010; Park et Friston, 2013; Raichle et al., 2006; Schmahmann et al., 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 et 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	Probabilistic	Seed	Native	Sphere	N/A	fMRI single-subject 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 audition	16	16	-	Healthy	60	HARDI	Probabilistic	Seed	Standard	Sphere	Displace ROIs	Reverse normalization

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, 2010a). 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 et al., 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 et al., 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 et Holloway, 2007; Powell et al., 2006, 2007; 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, 2010a). 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 et al., 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) (R. E. 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 et al., 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 (N=8)	5	5,5	2,21	2	11

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., 2006, 2007; Riley et al., 2015; D Saur et al., 2008; Dorothee Saur et al., 2010; Schott et al., 2011; Sitek et al., 2019; Takahashi et al., 2007; Thomalla et al., 2014; Umarova et al., 2010; Vry et al., 2012, 2015; 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 et al., 2011; Kim et al., 2005; Kleiser et al., 2010; Lanyon et al., 2009; D.-H. Lee et al., 2013, 2014; D. H. Lee et al., 2012; Lemaire et al., 2013; Mazerolle et al., 2010; Niu et al., 2016; Oguri et al., 2013; Pyles et al., 2013; L. B. Reid et al., 2016; L. B. Reid, Sale, et al., 2017; 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 et 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, 2010a).

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; D Saur et al., 2008; Dorothee Saur et al., 2010; Umarova et al., 2010; Vry et al., 2012, 2015). 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 et al., 2014; L. B. Reid et al., 2016; L. B. Reid, Pagnozzi, et al., 2017). 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, 2010a).

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., 2006, 2007; L. B. 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; D Saur et al., 2008; Dorothee Saur et al., 2010; Umarova et al., 2010; Vry et al., 2012, 2015). 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 et al., 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, 2010a). 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; L. B. 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:

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 (L. B. 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 et 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 et al., 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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Figures and references

Figure 1. – Schematic representation of the types of MRI modalities combination

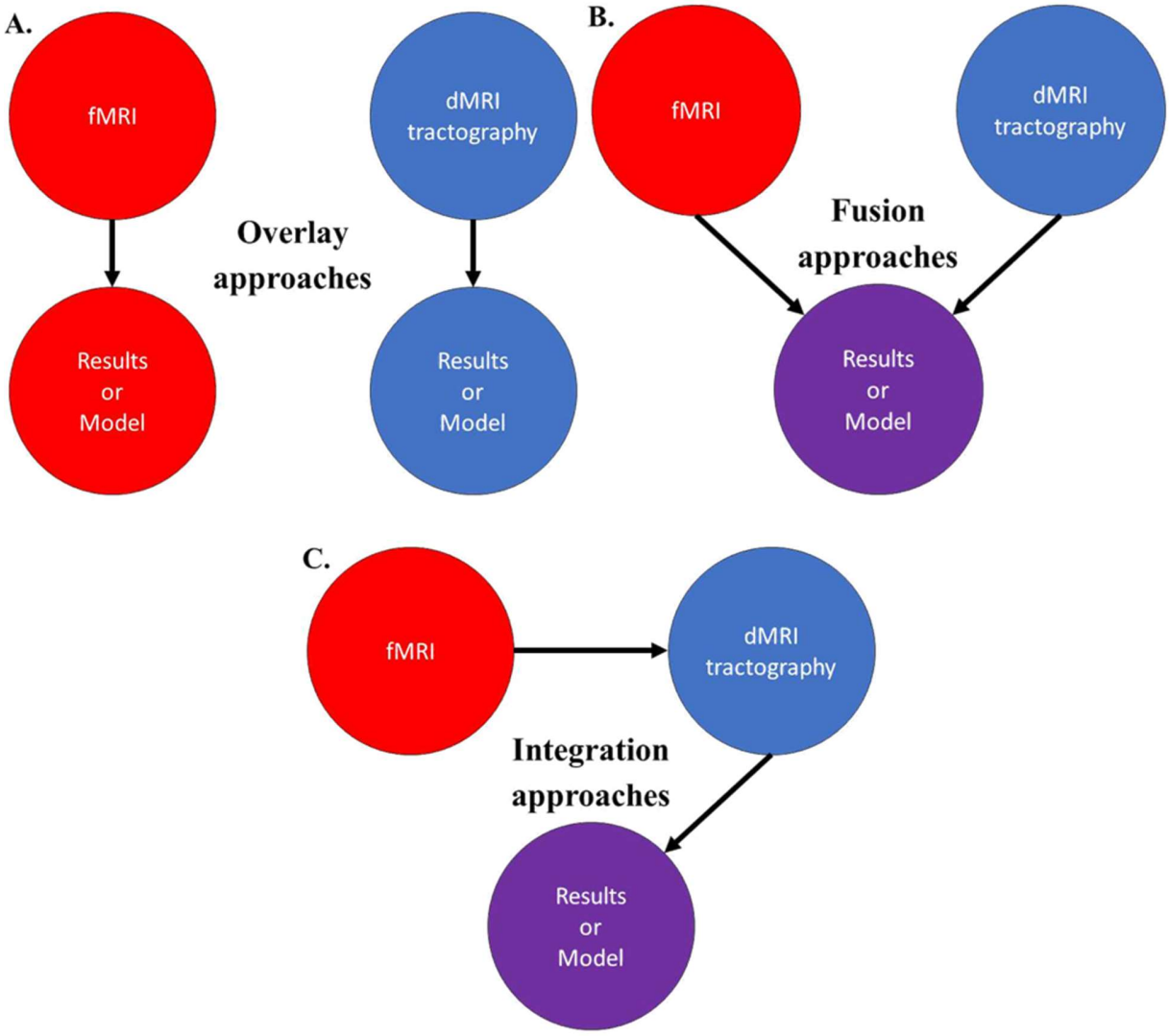


Figure 2. – PRISMA Flow Diagram for Scoping Review

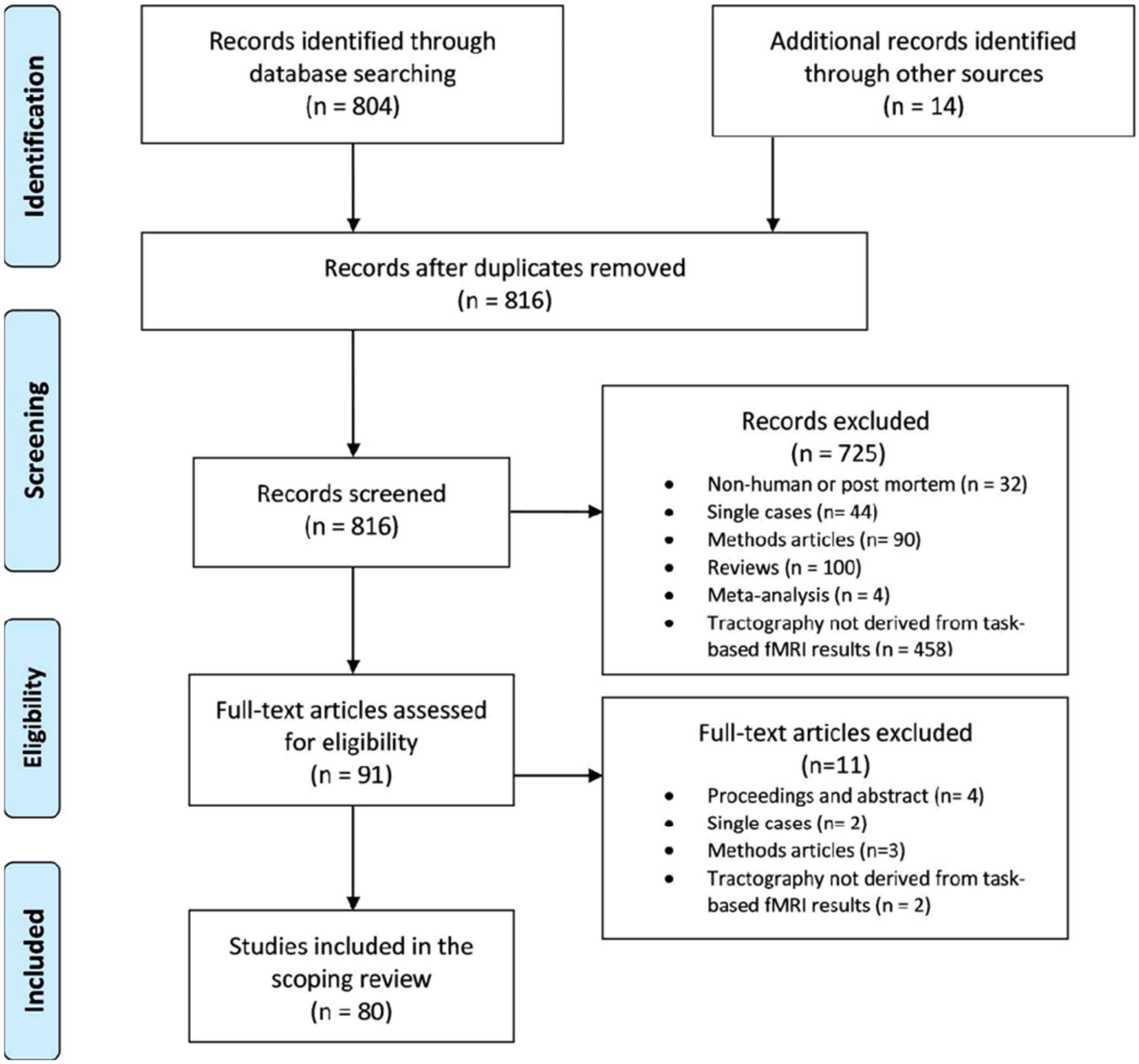
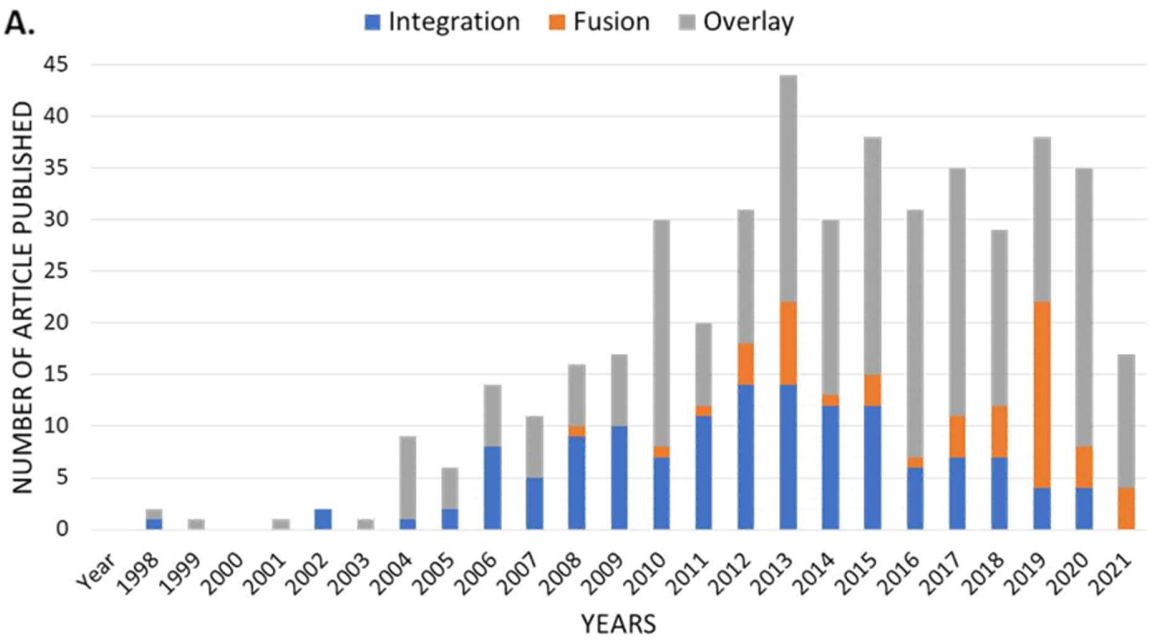


Figure 3. – **(A)** Number of studies that collected fMRI & dMRI data published per year sorted by combination types. **(B)** Repartition of studies that collected fMRI & dMRI data by combination types



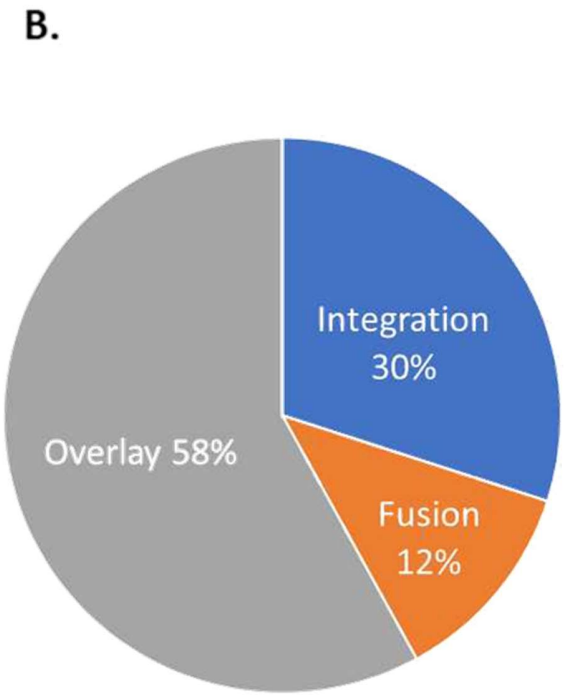


Figure 4. – Number of studies included published and their sample size sorted by the type of population investigated.

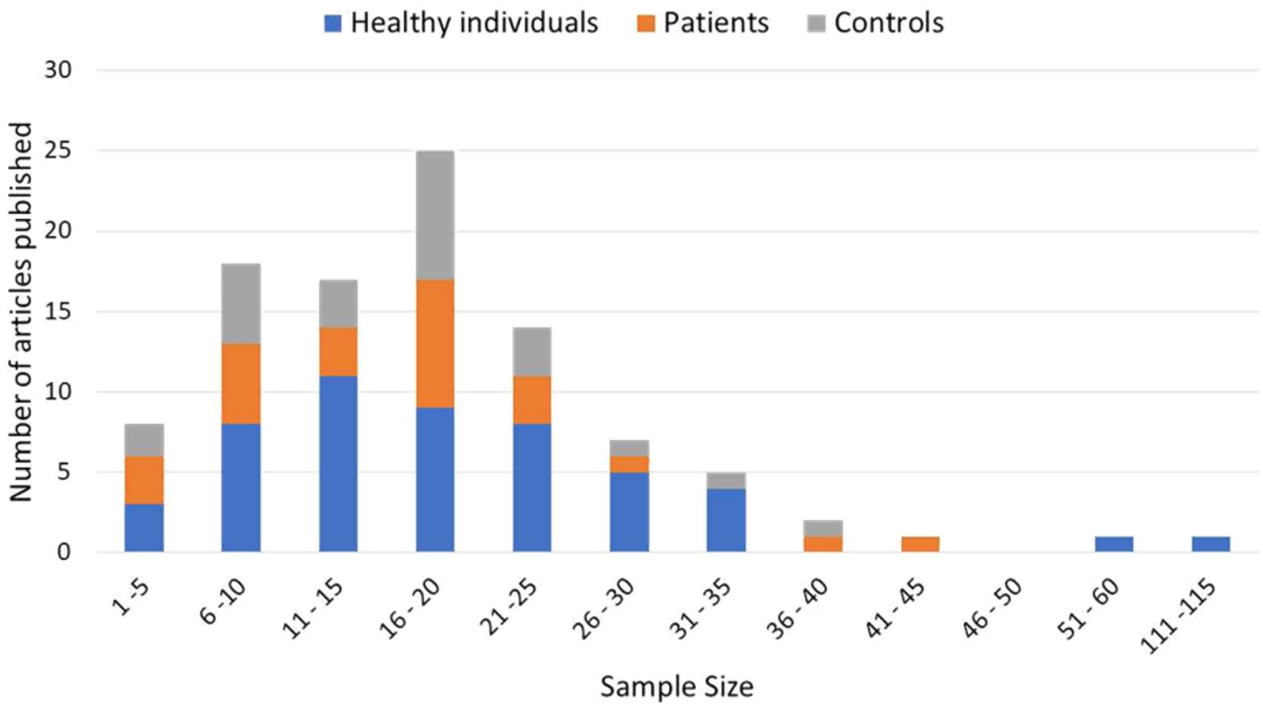


Figure 5. – **(A)** Repartition of diagnosis across included studies **(B)** Repartition of the neuroscientific domain investigated

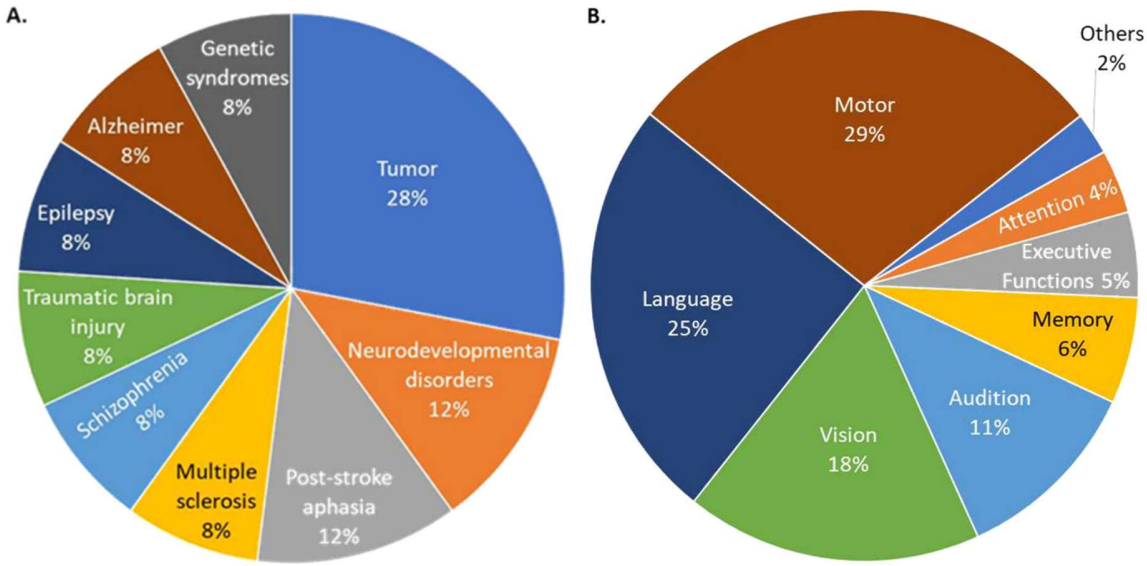


Figure 6. – Number of studies included published per years sorted by microstructure modelling category.

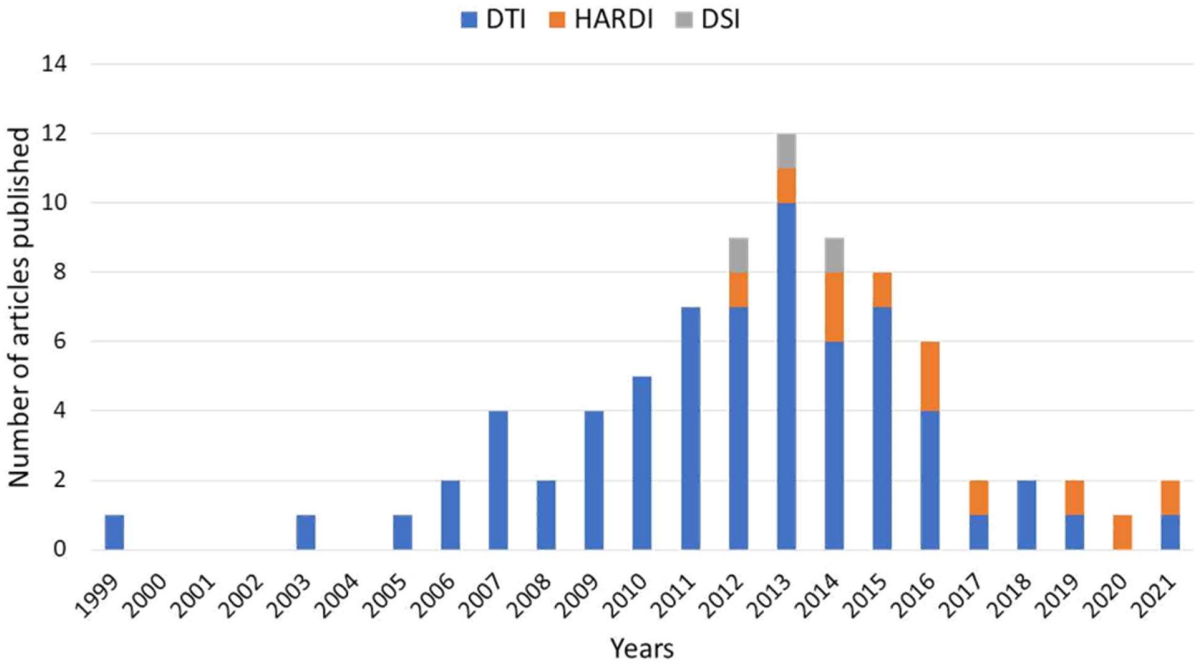
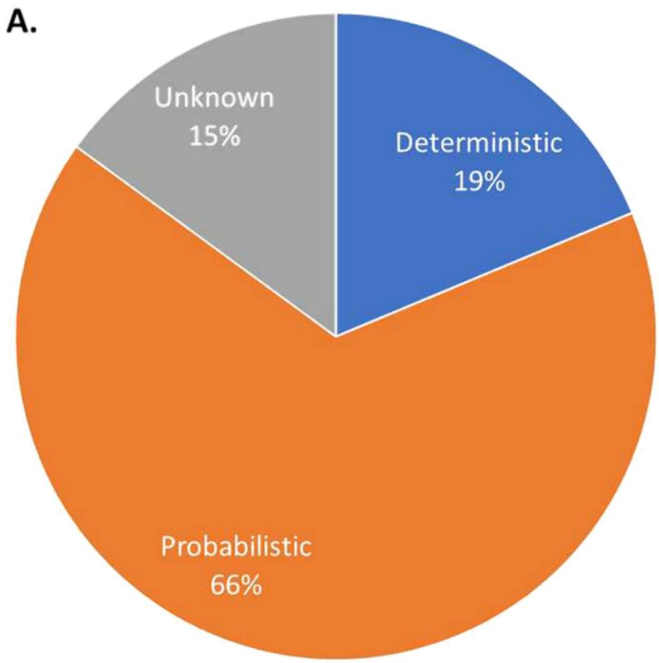
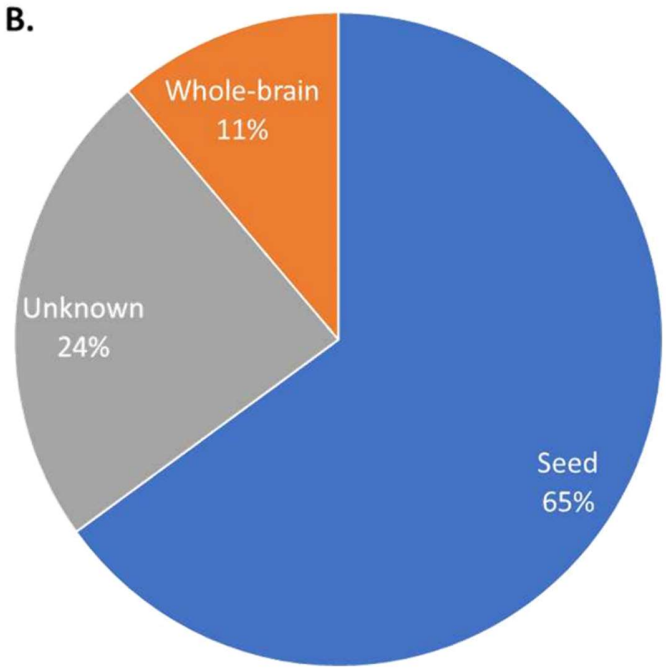


Figure 7. – **(A)** Repartition of tractography algorithm used across studies **(B)** Repartition of tractogram methods used across studies **(C)** Repartition of spaces used for tractography



A) 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



C.

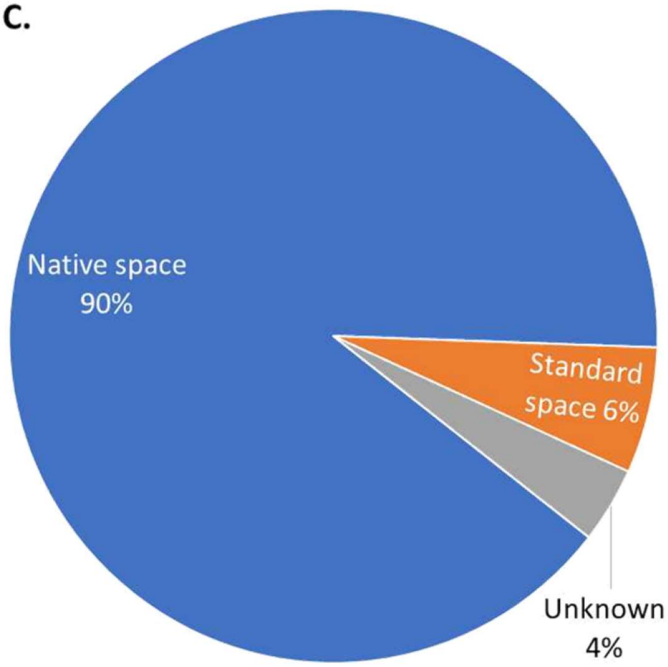
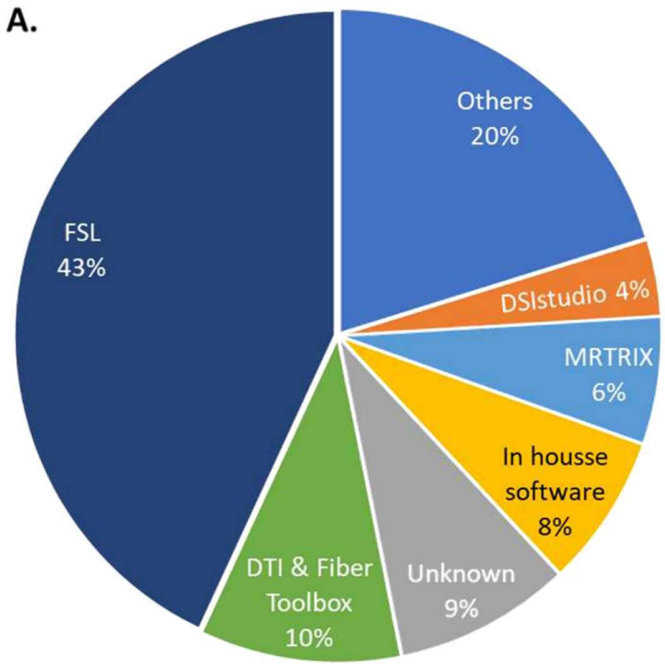
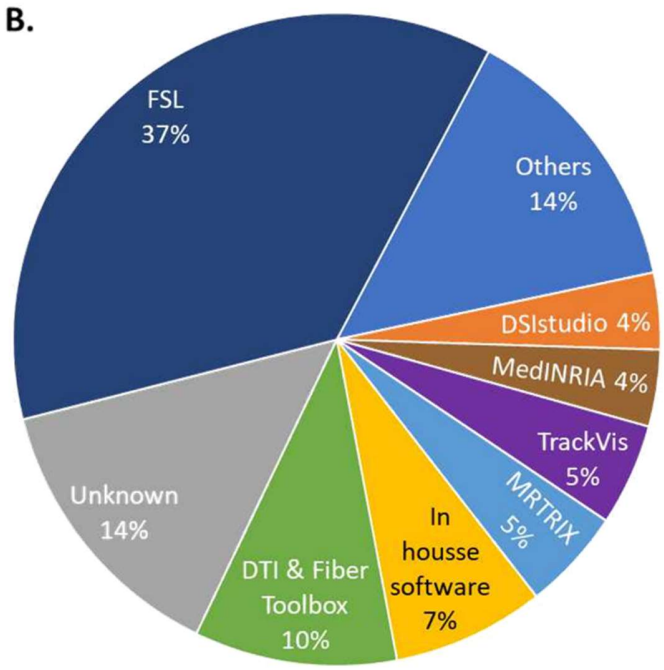


Figure 8. – **(A)** dMRI preprocessing software repartition. **(B)** Tractography software repartition. **(C)** fMRI software repartitions.



A) 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) 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.

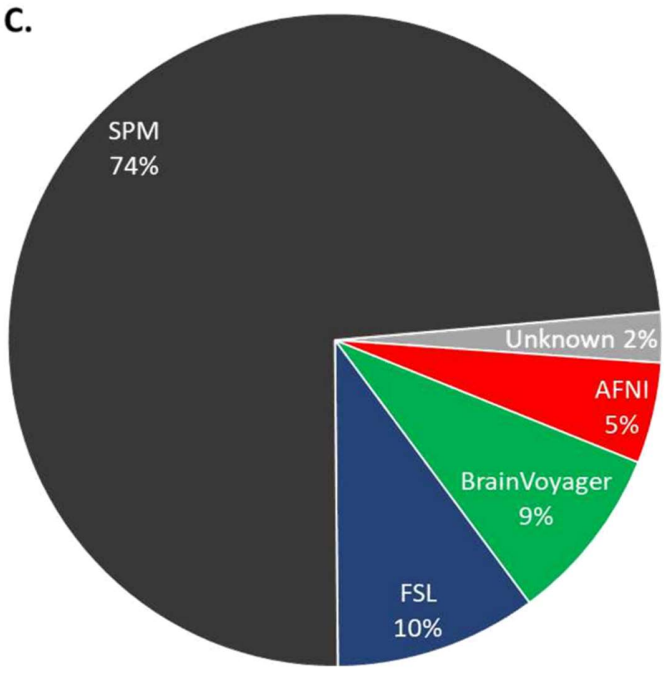


Figure 9. – **(A)** Repartition of the methods to derive seed region from task-based fMRI. **(B)** Repartition of methods used to match the fMRI and dMRI spaces. **(C)** Repartition of the methods to address the gray/white matter boundary

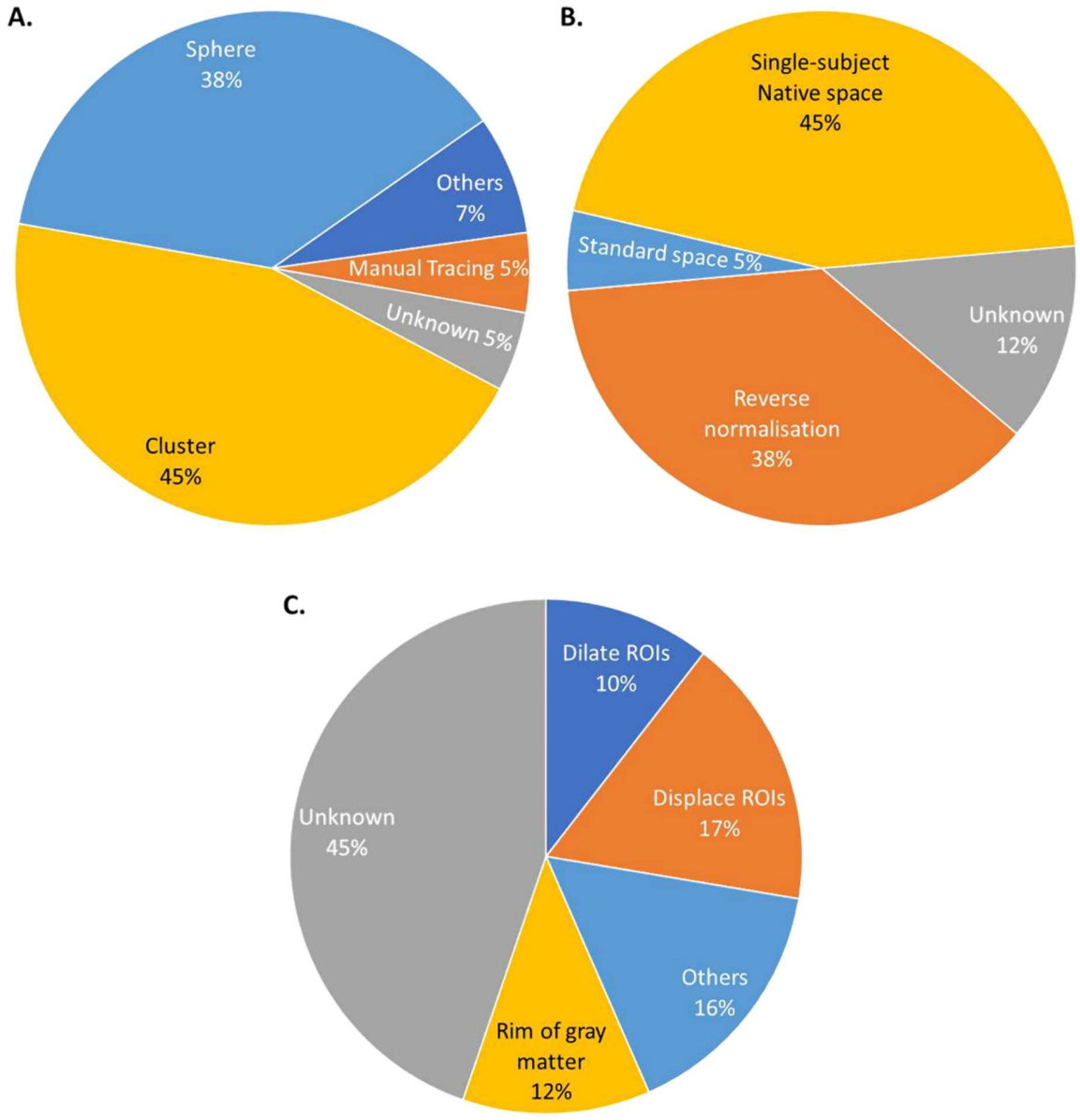
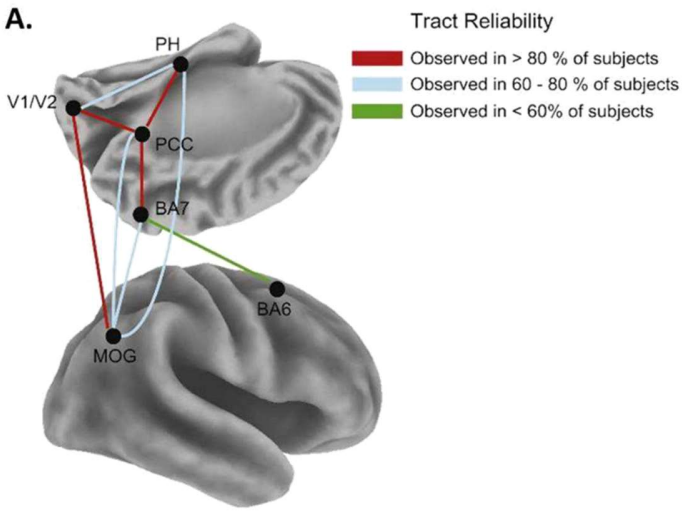
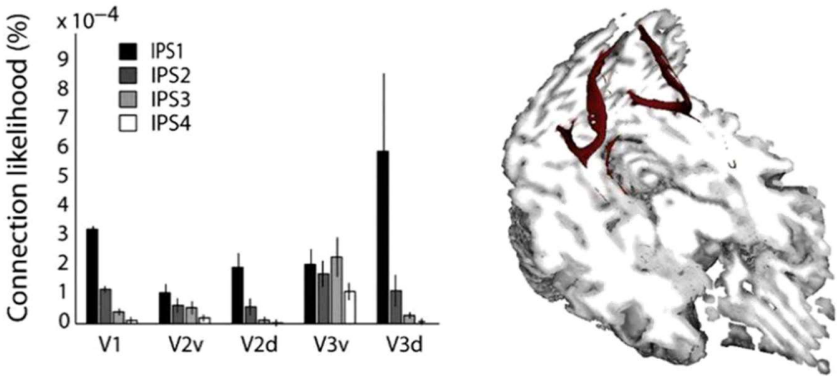


Figure 10. – Two examples of functionally derived fibre tracking data from multiple participants integrated in a group statistic while remaining in the participants native space.



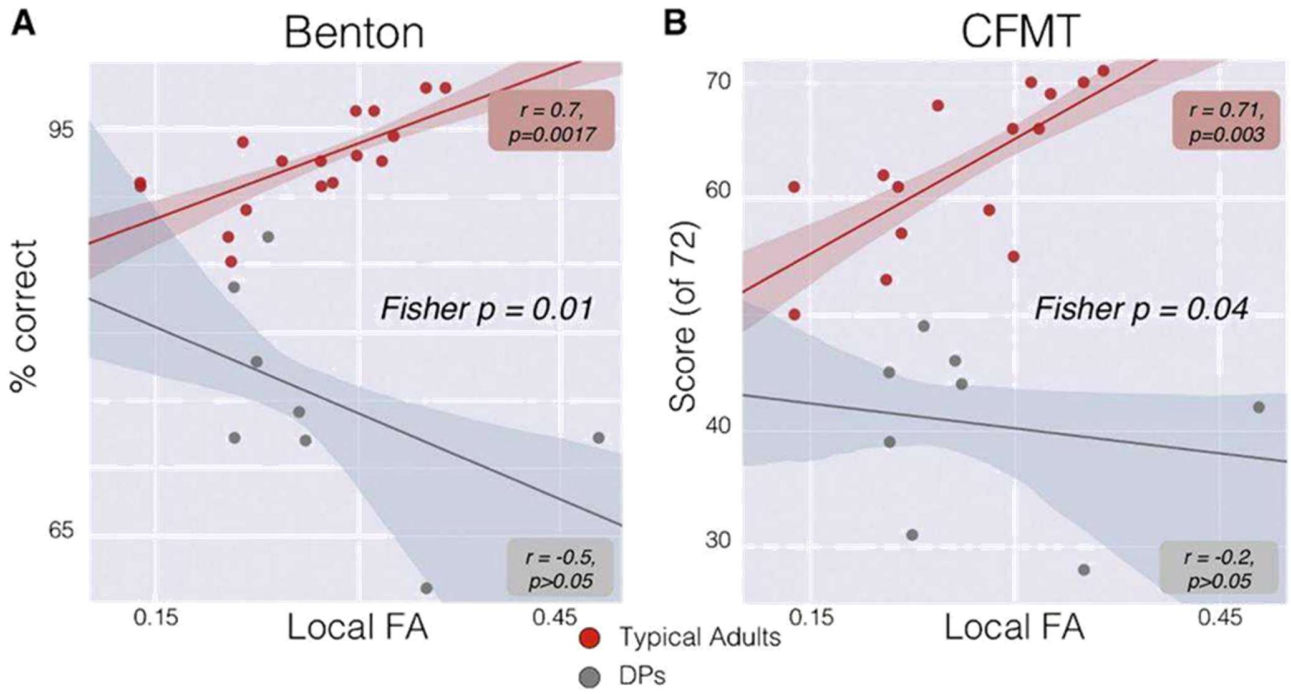
(A) Summary of anatomical connections underlying visuospatial imagery found in the Whittingstall et al., 2014 study. Connections in red represent those observed in over 80% of subjects. Reprinted fr m Cortex, vol. 56, Whittingstall et al., Structural network underlying visuospatial image y in humans, page 95, copyright 2013, with permission from Elsevier.

B.



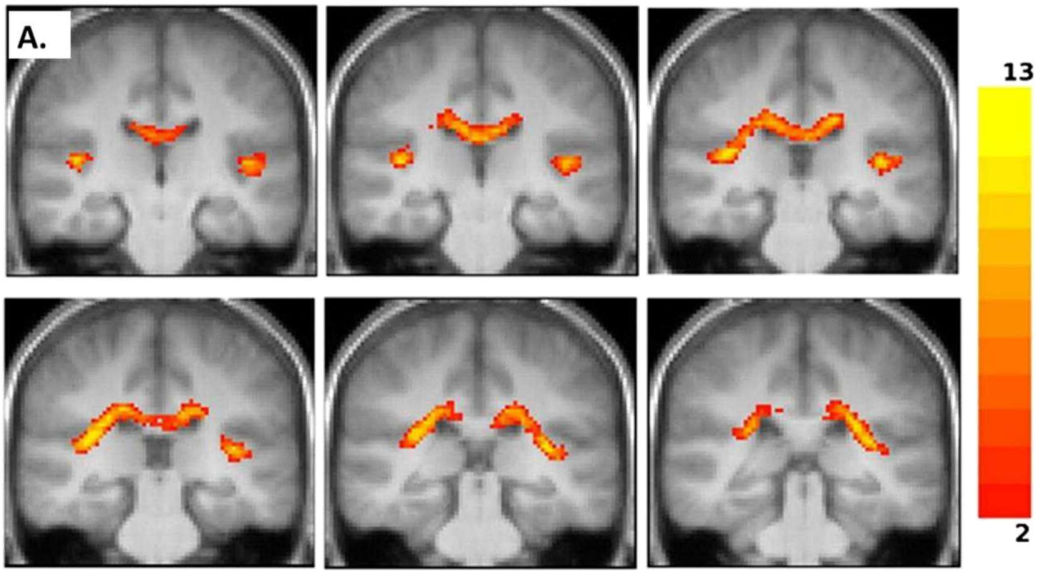
(B) Left: Left hemisphere int apa ietal sulcus topographic subregions (IPS1–4) connectivity to retinotopically defined striate and extrastriate visual regions. Right: Single participant illustrations of fiber tracking between IPS1 and V1. Reprinted from NeuroImage, vol. 82, Bray et al., Structural connectivity 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 participant's native space.

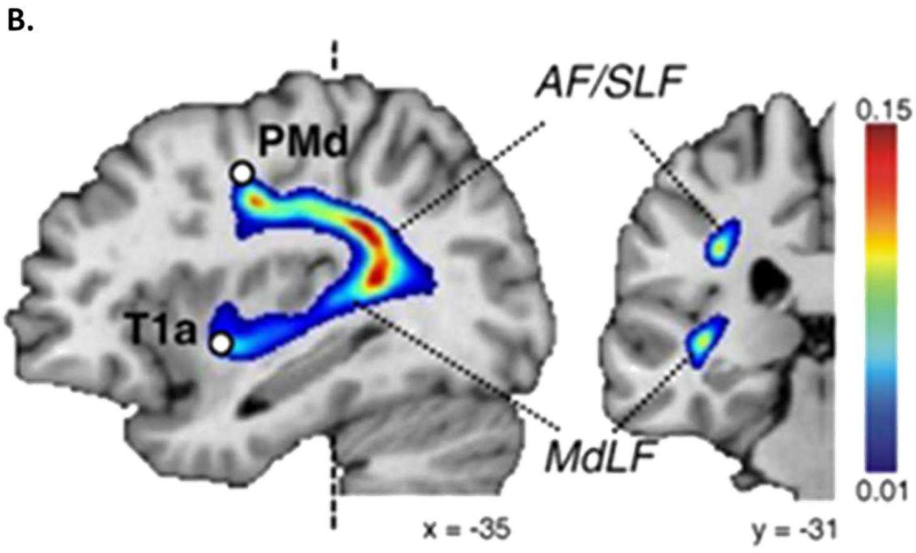


Correlations between the FA of a functionally defined white matter track and performance in face-processing tasks **(A)** Benton Face Recognition task (BENTON) and **(B)** the Cambridge Face Memory Test (CFMT)) in developmental prosopagnosia patients (DPs) and Typical Adults from Gomez et al., 2015 study. Reprinted from Neuron, vol. 85, Gomez et al., Functionally Defined White Matter Reveals Segregated Pathways in Human Vent al Temporal Cortex Associated with Category-Specific Processing, page 223, copyright 2015, with pe mission from Elsevier.

Figure 12. – Two examples of methods used to represent fibre bundles obtained in the participants native space in a c mm n 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 figures

Figure 1. – **(A)** Scanner field strengths repartition. **(B)** fMRI experimental design repartition.

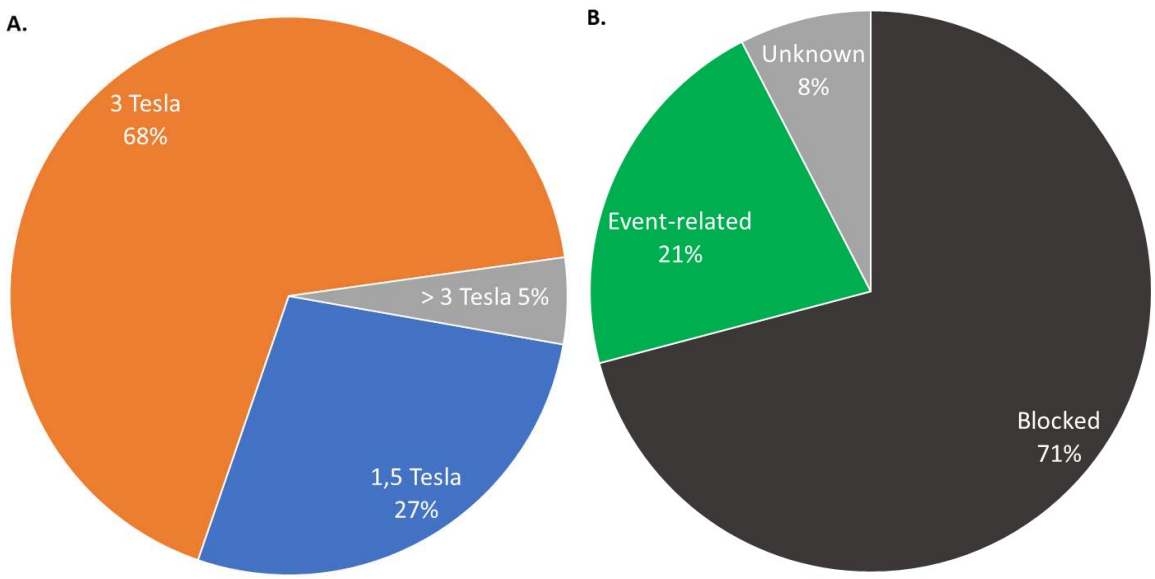
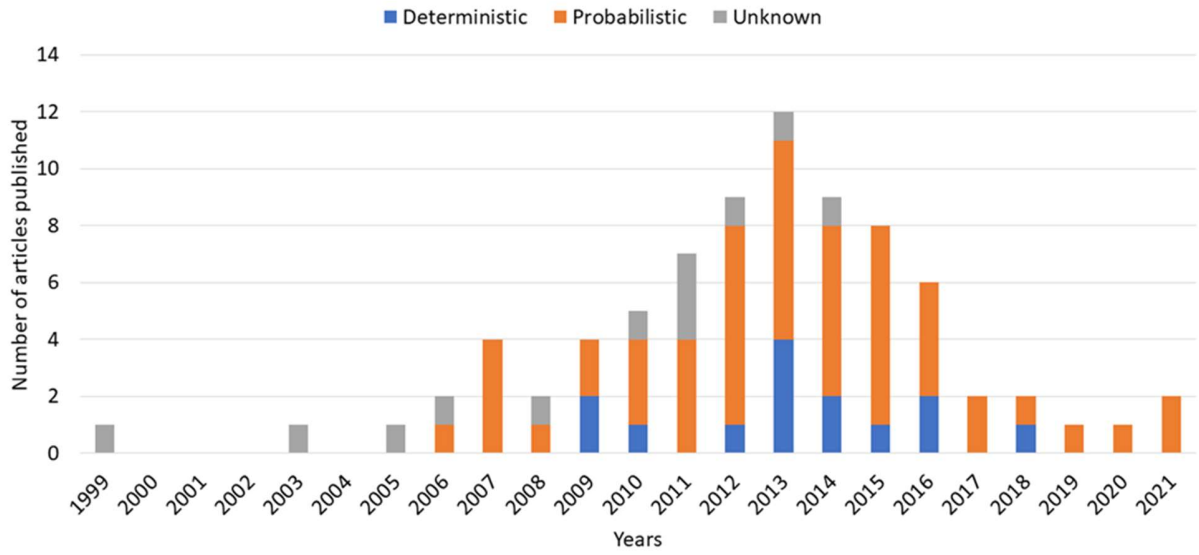


Figure 2. – Number of studies included published per years sorted by tractography algorithms.



CREDIT STATEMENT

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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

Article #2: Functional network and structural connections involved in picture naming

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Abstract:

We mapped the left hemisphere cortical regions and fiber bundles involved in picture naming in adults by integrating task-based fMRI with dMRI tractography.

We showed that a ventral pathway that "maps image and sound to meaning" involves the middle occipital, inferior temporal, superior temporal, inferior frontal gyri, and the temporal pole where a signal exchange is made possible by the inferior fronto-occipital, inferior longitudinal, middle longitudinal, uncinate fasciculi, and the extreme capsule.

A dorsal pathway that "maps sound to speech" implicates the inferior temporal, superior temporal, inferior frontal, precentral gyri, and the supplementary motor area where the arcuate fasciculus and the frontal aslant ensure intercommunication.

This study provides a neurocognitive model of picture naming and supports the hypothesis that the ventral indirect route passes through the temporal pole. This further supports the idea that the inferior and superior temporal gyri may play pivotal roles within the dual-stream framework of language.

Keywords: Functional MRI, tractography, diffusion MRI, multimodal neuroimaging, picture naming

1. Introduction:

The ability to name objects and concepts is one of the main aspects of human communication. Loss of this ability in neurological patients is associated with empty speech, major communication disorders, social isolation, and poor quality of life. It is common practice among healthcare professionals to explore the naming abilities of patients. Picture naming is the most widely used procedure to assess patients naming abilities, and various neuropsychological batteries include picture-naming assessments (Bortnik et al., 2013; Price, Devlin, Moore, Morton, & Laird, 2005; Strauss, Sherman, & Spreen, 2006). It is used for diagnostic purposes, to monitor patients' language during awake neurosurgery, and to follow up symptom evolution after a brain insult or language therapy (Bortnik et al., 2013; Coello et al., 2013; Fillingham, Sage, & Lambon Ralph, 2005; Lezak, Howieson, Loring, & Fischer, 2004; Price et al., 2005). However, information regarding the large-scale brain network involved in picture naming is still lacking, or at least a neuroanatomical model based on healthy subjects that include nodes and connections is still missing. Note that by brain networks we refer to the architecture that sustains cognitive functions where nodes of gray matter (neuronal cell bodies and synapses) communicate with each other via white matter pathways (myelinated and unmyelinated axons) (Catani & Ffytche, 2005; Jones, 2010; Mesulam, 1990). It is of major importance to healthcare professionals and the general cognitive neuroscientific community to better understand how the brain network involved in picture naming is implemented in healthy brains. The latter provides a theoretical framework to better understand naming impairments and anatomical damage in patients with neurological disorders.

Picture naming is the most widely used paradigm to rapidly tap into the various cognitive processes involved in everyday life production of speech (words) based on a visual stimulus. Picture naming requires perceptual integration, access to semantic memory (conceptual knowledge), phonological processing, and motor output planning (Price et al., 2005). Any disruption to these levels of the processing could potentially lead to object-naming deficits. This makes confrontational picture naming a practical tool to screen for cognitive impairments such as visual agnosia (visual object recognition deficit without language impairments), semantic memory deficits (loss of common knowledge), lexical access difficulty (word finding), paraphasic

productions (semantic and phonemic), and apraxia of speech (Price et al., 2005). These cognitive processes, or impairments, have all been associated with the ventral and dorsal streams of language, which theoretically implies that picture naming will recruit both.

1.1. The dual-stream framework in language

The framework of the dorsal and ventral streams (or pathway) of language was initially introduced for speech comprehension by Hickok and Poeppel in an analogous way to the dorsal (where/how) and ventral (what) streams of visual perception, as first described by Mishkin and Ungerleider (Goodale & Milner, 1992; Hickok & Poeppel, 2004; Mishkin, Ungerleider, & Macko, 1983). In this dual-loop framework of language, each pathway is anatomically well segregated but also double dissociated from a neuropsychological standpoint (see Hickok and Poeppel, 2004 for a review). The dorsal stream refers to the cortical region (grey matter) and fiber bundles (white matter) that are localized more dorsally and are also functionally involved in the process of "mapping sound to speech" (i.e., phonological processing and motor aspects of speech) (Hickok & Poeppel, 2004). On the other hand, the ventral stream of language is involved in the processing of "mapping sound onto meaning' (i.e., conceptual knowledge) (Hickok & Poeppel, 2004). As the name implies, it is localized to the ventral part of the cerebrum. Several studies support the idea that the dorsal stream of language is largely lateralized in the dominant hemisphere (the left hemisphere in the great majority of individuals). The ventral stream is somewhat less lateralized but shows a slight preference for the left hemisphere (Chang, Raygor, & Berger, 2015; Hickok & Poeppel, 2004; Parker et al., 2005; Pobric, Ralph, & Jefferies, 2009; Specht, 2013; Visser, Embleton, Jefferies, Parker, & Ralph, 2010; Weiller, Bormann, Kuemmerer, Musso, & Rijntjes, 2016).

1.2. Confrontational picture naming and grey matter

In 2005, Price et al. published a meta-analysis of PET and fMRI studies that made an important contribution to the description of brain regions involved in picture naming in healthy subjects. Their findings reported that picture naming involved an extended network that comprised brain regions associated with perception (i.e., occipital and posterior fusiform gyrus), speech production (i.e., inferior frontal gyrus pars opercularis, insula, cerebellum, and thalamus), and semantic/conceptual processes (i.e., anterior fusiform, temporal poles, and inferior frontal gyrus pars triangularis). Note that the latter tends to be in line with the aforementioned dual-stream

framework of language. These findings generally agree with studies that investigated neurological patients (i.e., neurodegenerative disease and post-stroke survivors) with naming impairments (see discussion for further details). Price et al. (2005) also highlighted that the baseline level of comparison of the picture-naming task had a major impact on the measured outcome. They showed that the lower-level baseline, which does not control for perceptual or speech production processes (i.e., fixation cross or a rest period), is well suited to detect extended brain activation related to perceptual and speech production processes while higher level baselines that control for speech production and perceptual processes (i.e., reading numbers or viewing images while saying "ok"), were better designed to isolate brain regions related to semantic/conceptual processing. As a concluding remark, it is worth mentioning that the picture naming studies analyzed by Price have used experimental sets of images and did not use stimuli from existing neuropsychological naming tests. The latter implies that some studies used specific categories of stimuli, such as plants, animals, or human-made artifacts/objects, while others used more than one category. In addition, the presentation mode was heterogeneous because stimuli were sometimes presented as photographs and sometimes as black and white drawings.

1.3. Associative white matter bundles involved in the language network

The topic of white matter pathway topography and its functional implications in cognition are extremely complex and can rapidly become overwhelming. Following this idea, Dick and Tremblay state that: "fiber bundles are not as distinct as the individualized names imply -while they can be identified and named, their spatial extent, origin, and termination are often difficult to establish-" (Dick & Tremblay, 2012). Note that this complexity was already appreciated by early anatomists, such as Reil (1809), Burdach (1822), Dejerine (1895), Trolard (1906), and Curran (1909). The latter should not be interpreted as a fatal indication that white matter fiber bundles are completely chaotic and disorganized, which makes them worthless to study. It reflects the actual state of knowledge in humans due to the inherent limitations of the different methods used to learn about fiber bundles. Indeed, comparative animal tracing studies using autoradiography (radioactive tracers) are considered the gold standard and extremely useful. However, the large evolutionary gap between human language and other species limits direct comparison, and support is needed from non-invasive and invasive methods in humans (i.e., diffusion MRI fiber tracking,

intraoperative direct electrical stimulation, and post-mortem human brain dissection) (Axer, 2011; Rilling et al., 2008). This article focuses exclusively on eight left-hemisphere white matter associative pathways that are commonly related to the language network. We first present fiber bundles forming the dorsal pathways, followed by the ventral bundles (see Fig. 1.).

1.4. Dorsal white matter bundles

1.4.1. The arcuate Fasciculus (AF)

The AF is known to connect posterior temporal areas such as the middle and superior temporal gyrus and some parts of the temporo-occipital junction to anterior frontal areas such as the inferior frontal gyrus and the ventrolateral premotor cortex. Topographically, it arched around the Sylvian fissure. It is located ventral to the superior longitudinal fasciculus (SLF) (Axer, Klingner, & Prescher, 2013; Burdach, 1822; Catani, Jones, & Ffytche, 2005; Dejerine, 1895; Geschwind, 1965; Makris et al., 2005; Nishitani, Schurmann, Amunts, & Hari, 2005; Petrides, 2013; Reil, 1809).

1.4.2. The Superior longitudinal fasciculus (SLF)

The SLF is divided into three major branches (SLF-I, SLF-II, and SLF-III), connecting most of the parietal lobe to the frontal lobe (Makris et al., 2005; Petrides, 2013; Schmahmann & Pandya, 2006d). Please note that These subcomponents are subject to controversy (see Wang et al., 2016). However, we will not cover the SLF subdivisions in detail because their contribution to picture naming is less established, and they are more involved in other cognitive functions, such as visuospatial processing, spatial attention, somatosensory processing, and gesture production. If the reader is interested in knowing more about how we performed the in vivo dissection of the SLFs in this study, please refer to the supplementary material, where the white matter queries used can be found. For more information on this topic, we refer the reader to previous articles/reviews (Frey, Campbell, Pike, & Petrides, 2008; Makris et al., 2005; Petrides, 2013; Schmahmann & Pandya, 2006d; Wang et al., 2016).

1.4.3. Frontal aslant tract (FAT)

The FAT was first described in the last decade as a short-range ascending association fiber and is thought to connect the medial frontal cortex (i.e., superior frontal gyrus, SMA, and pre-SMA) to the posterior part of the inferior frontal gyrus (Catani et al., 2012; Dick, Bernal, & Tremblay, 2013).

1.4.4. Involvement of dorsal fiber bundles in language:

In classic aphasiology studies, Geschwind and other pioneers clearly established the involvement of the AF in conduction aphasia syndrome (Benson et al., 1973; Damasio & Damasio, 1980; Geschwind, 1965; Goodglass & Kaplan, 1972). Later on, research has shown that stimulating AF induces phonemic paraphasia during picture naming (Duffau, Gatignol, Denvil, Lopes, & Capelle, 2003; Duffau, Moritz-Gasser, & Mandonnet, 2013; Sarubbo et al., 2015). Similarly, investigation of logopenic primary progressive aphasia (lv-PPA) and non-fluent primary progressive aphasia (nv-PPA) patients reported significant microstructural changes within the AF (Galantucci et al., 2011). Saur et al. (2008) integrated fMRI and dMRI tractography to provide evidence that brain regions activated during sublexical (pseudoword) repetition were linked by the left AF. Kinoshita et al. (2015) suggested that intraoperative direct electrical stimulation of the left hemisphere FAT induces interruption of speech during verbal fluency (phonemic or semantic), as it connects the pars opercularis to the pre-SMA. Evidence from fMRI and tractography also supports the idea that FAT is involved in speech initiation and verbal fluency (see Dick et al., 2019 for a review).

1.5. Ventral white matter bundles

1.5.1. Inferior longitudinal fasciculus (ILF)

The ILF is a long association fiber that runs along the occipital lobe and ventral temporal lobe (Axer et al., 2013; Burdach, 1822; Catani & de Schotten, 2012; Reil, 1809; Schmahmann & Pandya, 2006b). Tracing studies in rhesus monkeys suggest that the ILF also reaches the parietal lobe. However, most of the ILF concerns occipitotemporal connections (Schmahmann & Pandya, 2006b).

1.5.2. Middle longitudinal fascicle (MdLF)

The MdLF connects the superior parietal lobule and inferior parietal lobule with the superior temporal gyrus and temporal pole (Axer et al., 2013; Makris et al., 2013; Makris et al., 2009; Schmahmann & Pandya, 2006c; Seltzer & Pandya, 1984). The parietal/posterior part of the MdLF is localized medioventrally in relation to the SLF-II and AF. The temporal/anterior part of the MdLF runs dorsally along the dorsal part of the temporal lobe white matter (Makris et al., 2013; Makris et al., 2009; Seltzer & Pandya, 1984).

1.5.3. Inferior fronto-occipital fascicle (IFOF)

The IFOF runs from the occipital lobe and inferior posterior-temporal cortex to the inferior frontal gyrus and orbitofrontal cortex. It passes across the temporal lobe white matter dorsally to the ILF and then reaches out to the frontal lobe by passing between the insula and the claustrum (Catani & Thiebaut de Schotten, 2008; Curran, 1909; Fernández-Miranda, Rhoton, Kakizawa, Choi, & Álvarez-Linera, 2008; Martino, Vergani, Robles, & Duffau, 2010; Petrides, 2013).

1.5.4. Extreme capsule fasciculus (emC)

The emC connects the middle superior temporal gyrus and inferior parietal lobule (angular gyrus) with the ventrolateral prefrontal cortex (Brodman areas 44, 45, and 47). It passes across the dorsal white matter of the temporal lobe and extends towards the frontal lobe by sneaking between the insula and claustrum (Axer et al., 2013; Frey et al., 2008; Makris & Pandya, 2009; Petrides & Pandya, 1988; Petrides, 2013; Schmahmann & Pandya, 2006a).

1.5.6. Uncinate fasciculus (UF)

The UF connects the anterior temporal lobe, parahippocampal gyrus, and amygdala with the medial and orbital prefrontal cortex and pars orbitalis of the inferior frontal gyrus (Axer et al., 2013; Catani & de Schotten, 2012; Fernández-Miranda et al., 2008; Reil, 1809; Schmahmann & Pandya, 2006e). Its hooked shape is characteristic of this fiber bundle that arches from the anterior temporal to the orbitofrontal cortex by passing between the insula and the claustrum, similar to the IFOF and emC. However, at the level of the insula and claustrum, the IFOF, UF, and emC are difficult to distinguish using non-invasive means (i.e., dMRI tractography) (Axer et al., 2013). The UF is expected to be the most ventral part, with the emC being the most dorsal part, as the IFOF stands in between (Axer et al., 2013; Fernández-Miranda et al., 2008).

1.5.7. Involvement of ventral fiber bundles in language:

It has been hypothesized that the ILF and UF might act together as an indirect route in the ventral stream of language (Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007; Vigneau et al., 2006), but surprisingly the direct electrical stimulation of the ILF or UF does not appear to impair picture naming (Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009; Mandonnet et al., 2007). The latter hypothesis is supported by Galantucci et al. (2011) and Agosta et al. (2010), who showed

microstructural changes in the ILF and UF among patients with semantic variant primary progressive aphasia (sv-PPA). Furthermore, Shinoura et al. (2010) investigated a patient who had a previous left IFOF lesion and presented with worsening picture-naming ability after a second lesion to the left ILF. In her work, Papagno gathers converging evidence from patients with temporal lope epilepsy, patients who underwent UF resection due to tumor infiltration plus MRI data from normal and pathological aging (i.e., neurodegenerative diseases) and concludes that the left UF could potentially be involved in naming famous people as this task is more challenging than picture naming (i.e., unique entities VS. non-unique entities) (Papagno, 2011; Papagno et al., 2011).

The implication of the MdLF in language remains to be clarified because of recent controversies (see De Witt Hamer et al., 2011; Turken and Dronkers, 2011 for more details). However, Sarubbo et al. (2015) reported interesting cases of pure anomia during picture naming when direct electrical stimulation was applied at the posterior part of the MdLF.

To the best of our knowledge, no intraoperative direct electrical stimulation study has investigated emCs. However, Saur et al. (2008) integrated fMRI and dMRI tractography to provide evidence that brain regions activated during auditory sentence comprehension are mainly connected via the left extreme capsule. Finally, intraoperative direct electrical stimulation of the IFOF during picture naming systematically induces semantic paraphasia (De Witt Hamer et al., 2011; Duffau, Moritz-Gasser, et al., 2013; Sarubbo et al., 2015). It was hypothesized that the IFOF serves as a direct route between the visual object recognition centers and prefrontal language cortices (Duffau, Moritz-Gasser, et al., 2013).

1.6. The gap in the literature

Most knowledge regarding the structural connection underlying the language network is derived from brain-damaged patient studies (which include intraoperative direct electrical stimulation). Although patient data are insightful, they present some limitations, as most patients suffer damage to more than one module and present considerable differences in terms of age, expertise, and education. Furthermore, we cannot always assume that the cognitive performance or the neural organization of patients with brain damage provides direct evidence of the impact

of the lesion as there can be premorbid alterations that are amplified by a more recent brain insult. These limitations can be addressed in part by convergent evidence from healthy individuals. Few studies have investigated the typical functional and structural connections involved in neuropsychological tests assessing picture naming in healthy adults. To our knowledge, only one article has integrated task-based fMRI activation from a picture-naming test (Philadelphia Naming Test) to guide dMRI fiber tracking (Xing et al., 2018). They found that 14 left hemisphere tracks (initially identified in healthy adults) and microstructural properties (i.e., fractional anisotropy) were significantly related to post-stroke aphasic patient picture naming scores. However, their study lacked information about the topographical organization of these fiber tracks and did not label their fiber tracking results according to known white matter structures (i.e., from an atlas). As we report in our scoping review, it is quite frequent that studies integrating task-based fMRI to guide dMRI fiber tracking omit labeling their fiber tracking results (Jarret, Bore, Bedetti, Descoteaux, & Brambati, 2021). The latter is problematic because the fiber tracks remain "unidentified" which precludes the establishment of a clear relationship between the function and the concerned white matter label.

1.7. Aims

Our study aimed to investigate the brain network involved in the execution of confrontation picture-naming tests in healthy adults. Our objectives were: **1)** to describe the brain's functional network involved in the most frequently used test to assess picture naming abilities, the Boston Naming Test (BNT) (Bortnik et al., 2013; Strauss et al., 2006) **2)** to determine the topography of the left hemisphere white matter fiber tracks that interconnect the functional network nodes; and **3)** to verify if these fiber tracks are part of a known white matter structure or segregated from it.

1.8. Relevance

This article provides a reference model for the functional network involved in the execution of the BNT in healthy adults and its underlying structural connections that guarantee signal transmission across the concerned brain regions. This information is relevant for neuropsychologists, speech therapists, neurosurgeons, and other healthcare professionals who assess naming impairments in patients.

1.9. Hypothesis

We expected brain activation similar to that described by Price et al. (2005) in their meta-analysis. We hypothesize that the BNT recruits both the dorsal and ventral streams of language. More precisely, we expect that, in the ventral stream, both the direct (IFOF and emC) and indirect (ILF and UF) routes will be recruited to name the pictures. For the dorsal stream of language, we believe that the only bundles recruited will be the AF and FAT.

2. METHODS:

2.1. Participants

We recruited 37 right-handed native French-Canadian speakers (15 males and 22 females from 18 to 35 years with a mean age of 26.19 ± 4,9 years and a mean education level of 14,9 ± 3,5 years). They had normal or corrected vision and no history of neurological or psychiatric disorders. Right manual laterality was confirmed using the Edinburgh Handedness Inventory (Oldfield 1971). This study was approved by the local ethical committees (Comité d'éthique de la recherche vieillissement-neuroimagerie du Centre intégré universitaire de santé et de services sociaux du Centre sud de l'Ile de Montréal) and all participants gave written informed consent prior to their participation. Table 1 summarizes the sociodemographic characteristics of the participants.

Table 1: Sociodemographic characteristics

Sociodemographic characteristics (N=37)	**Mean or %**	**SD**
Age	26.19 (M)	4.9
Sex		
Men	48 %	
Women	57%	
Education level completed		
Highschool not completed	10 %	
Highschool, College or vocational school	29 %	
University	61 %	
Handedness (Edinburgh)		
Laterality index	0,90	0,11

2.2. Experimental Tasks

During fMRI acquisition, participants completed the BNT (Kaplan, Goodglass, & Weintraub, 1983; Roberts & Doucet, 2011). The purpose of the BNT is to assess naming ability from visual input using 60 black and white drawings of everyday objects and animals (Kaplan et al., 1983; Strauss et al., 2006). We chose the BNT because it is among the most frequently used tests to assess naming ability; it is used for diagnostic purposes, to monitor patients' language during awaken neurosurgery, and to follow up symptom evolution after a brain insult recuperation or language therapy (Bortnik et al., 2013; Coello et al., 2013; Fillingham et al., 2005; Lezak et al., 2004; Price et al., 2005). It is also validated for our French-speaking sample (Roberts & Doucet, 2011).

2.2.1. Boston Naming Test (BNT) fMRI paradigm:

We presented stimuli in a block-design fashion to increase signal detection power. Blocks were alternated with fixation cross blocks (baseline level) for contrast analysis. Note that we deliberately chose a non-specific or low-level baseline (fixation cross) to capture the extended networks associated with the task (i.e., visual network and speech production activity) (Price et al., 2005). Each BNT stimulus was visually presented for 1500 ms, and participants had an extra 1500 ms to give their answers verbally (overt) before the next trial (see Figure 2 for an example of the procedure). The timing parameters of the stimuli presentation were based on preliminary unpublished pilot behavioral data obtained from our laboratory. The stimuli were separated by an inter-stimulus interval lasting 350 ms where a blinking fixation cross indicated that the trial had finished. This task comprised 12 blocks of five drawings to name for 17.5 seconds each. The naming blocks were separated by 12 fixation cross blocks, each lasting 17.5 seconds for a total of 145 volumes. Stimuli were presented in the same order for each participant. Note that we did not respect the standardized stimuli presentation order of the test because we also wanted to contrast items that had a higher complexity level with items that had a lower complexity level (a composite of lexical frequency and success rate from Roberts and Doucet, 2011). However, this procedure was unfruitful and did not yield significant results; therefore, it will not be addressed further in this article.

We opted for an overt vocalization production mode because we needed to record task performance for behavioral analysis and monitor the participants' compliance during the tasks.

Participants were asked to name the images they saw on the screen as soon as possible during the fMRI acquisition. They were instructed to limit their movement as much as possible, and a practice session was performed before the scanning session to ensure that they knew how to limit their head movement when producing overt speech. They were also asked to give answers that contained only a single word (i.e., “pen” vs. “This is a pen”) and restrain to answer if they didn’t have the exact word in mind (i.e., “It is for writing” vs. “pen”).

The BNT stimuli were presented using the DMDX presentation software (Forster & Forster, 2003). Response accuracy and response time were corrected offline using Checkvocal software (Protopapas, 2006). Answers were considered good only if they fit the French translation or synonyms provided by Roberts and Doucet (2011), whereas answers were considered wrong if they did not fit the latter or if the participant did not vocalize an answer during the stimulus trial (3 s). In this study, we focused exclusively on participants who gave > 60% correct answers during the fMRI BNT session. The latter could be criticized because we might omit a part of the population by doing so. However, it was necessary to exclude participants who were less compliant or had unknown/idiopathic naming difficulties (i.e., possible undiagnosed specific developmental language disorder). Furthermore, this choice was guided by our intention to map the functional and structural networks at work during the efficient performance of the BNT.

2.3. MRI data acquisition and processing

We acquired MRI images using a 32-channel head coil and a 3T SIEMENS Tim Trio magnetic resonance imaging system (Siemens, Erlangen, Germany) between August 2015 and October 2016. The head movements were limited to the head coil using foam rubber pads. The participants had a microphone aligned with their mouth to allow for vocal recordings (*MRConfon*^{TM}). All dummy scans were automatically removed during the MRI data acquisition session to allow for the T1-equilibration effect.

High-resolution anatomical images (T1) were acquired with a Multi Echo Multi Planar Rapid Gradient Echo (MEMPRAGE) pulse sequence and a GRAPPA acceleration factor of 2 using the following parameters: FoV 256.0 mm^2, matrix size 256 × 256, 176 slices covering the whole brain, 1 mm isotropic voxel size, TE/TR = 1.64/253 ms, flip angle 7.0°.

Functional images (T2*) were acquired with echo-planar imaging (EPI) pulse sequence and a GRAPPA acceleration factor of 2 using the following parameters: FoV 220 mm^2, matrix size 74 × 74, 50 ascending slices covering the whole brain, 3 mm isotropic voxel size, TR/TE= 3000/20 ms, flip angle 90°. T2* image acquisition was oriented -30° from the AC-PC line (to reduce the anterior temporal lobes and orbitofrontal cortex signal loss) (Devlin et al., 2000). A continuous sampling method was used, and field maps were acquired to allow susceptibility artifact distortion correction.

Diffusion-weighted images (DWI) were acquired with a single-shot spin echo-planar imaging pulse sequence and a GRAPPA acceleration factor of 2 using the following parameters: FoV 240.0 mm^2, matrix size 120 × 120, 66 interleaved slices covering the whole brain, 2 mm isotropic voxel size, TR/TE = 9100/94 ms, flip angle 180.0°. DWI was acquired along 64 independent directions with a b-value of 1000 s/mm^2. A pair of b0 images with no diffusion weighting and opposite phase encoding polarity were acquired to allow susceptibility artifact distortion correction.

MRI data preprocessing and analysis

Fig. 3 summarizes the great steps of multimodal MRI data processing, analysis and integration.

2.3.1. fMRI Preprocessing

We performed fMRI data preprocessing and statistical analysis in SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) running MATLAB 2012a (MathWorks, USA). First, we visually inspected the fMRI images to ensure that there were no artifacts or that brain coverage was missing. We then applied slice-timing correction, spatial realignment, and images unwarped using field map images to compensate for nonlinear distortions caused by magnetic field inhomogeneity and transient head movement. All corrected fMRI volumes were co-registered with the participants' DWI undistorted native spaces. Tissue segmentation was applied to each T1 image, and the inverse direction deformation field was saved to allow future inverse normalization of the functionally defined ROIs in the participant's original DWI undistorted native space. Functional images were normalized to the MNI space template and smoothed with a 6 mm FWHM Gaussian kernel. We used the ArtRepair toolbox (Mazaika, Hoeft, Glover, & Reiss, 2009; Mazaika, Whitfield, Cooper, Mazaika, & Whitfield…, 2005) to detect outlier volumes showing ≥0.9

mm/degree root mean squared volume-to-volume head movement (translation or rotation). We excluded participants from the fMRI analysis if ≥20% of their volumes were outliers or if they showed a total head movement greater than a voxel size (±3 mm translation or ±3°of rotation). Based on this criterion, 2 participants were excluded from the study.

2.3.2. fMRI Statistical analysis

The onset and duration of stimuli were modeled at the first level and convolved with a canonical hemodynamic response function (HRF), as implemented in SPM12 for each participant. Realignment parameters and movement outliers detected by ART were included as covariates of no interest in the general linear model (GLM). We compared picture naming (BNT) with a fixation cross (baseline). We then performed a second-level random-effects analysis on the contrast images. We used a threshold corrected for multiple comparisons at the voxel level of $p < 0.05$ (FWE) as implemented in SPM12 (random field theory), with a cluster extent of $K \geq 30$ (Worsley, Cao, Paus, Petrides, & Evans, 1998). We labeled the brain activation coordinates according to the probabilistic SPM Anatomy Toolbox Atlas (Eickhoff et al., 2005).

2.3.3. DWI Preprocessing

Next, we denoised DWIs using the local principal component analysis (LPCA) method (Manjo et al., 2013). We corrected DWIs for eddy currents, head motion, and susceptibility artifacts using FSL Eddy and TOPUP (FMRIB Analysis Group; Oxford, United Kingdom FSL, http://www.fmrib.ox.ac.uk/fsl) (Andersson, Skare, & Ashburner, 2003). The gradient directions were corrected using the corresponding motion correction parameters (Jones & Cercignani, 2010). Fourth, we upsampled motion-corrected DWIs using cubic interpolation (upsampling to T1 anatomical resolution). T1 anatomical images were registered to the corresponding participant's corrected/undistorted DWI. We sent the anatomical images through the Freesurfer pipeline (Dale, Fischl, & Sereno, 1999) to use the five-tissue-type segmentation (5TT) in the latter Anatomically Constrained Tractography step (ACT) (Smith, Tournier, Calamante, & Connelly, 2012). We used MRtrix3 (https://www.mrtrix.org/) to reconstruct the fiber orientation distribution function (fODF). We estimated the response function for a single fiber population using Tournier's algorithm (Smith et al., 2012). We used this response function to estimate the fiber orientation distribution (FOD) for each voxel using constrained spherical deconvolution

(CSD) (Tournier, Calamante, & Connelly, 2007) with a maximum spherical harmonic order Lmax of 8.

2.3.4. Functionally defined regions of interest (ROIs) for fiber tracking

To generate functionally defined ROIs to guide fiber tracking analysis, we first inversely normalized the left hemisphere cortical peak fMRI coordinates of each activated cluster in the participant's undistorted DWI natives' space. This was performed using the parameters obtained during the segmentation procedure of the T1 anatomical scan. Second, we generated a 5-mm radius sphere on the corresponding coordinates. This sphere radius was based on the results of our methodological review (Jarret et al., 2021). Third, we inspected each sphere to ensure that they were in contact with the participants using a gray and white matter interface mask.

2.3.5. DWI Fibre tracking

For each fiber tracking procedure, we used the ACT (Smith et al., 2012) algorithm implemented in MRtrix3. We threshold maximum step size at 0.5 voxel size, maximum curvature of 45°, and maximum track length of 300 mm, as suggested in the MRtrix documentation. For the fiber tracking of pathways that interconnect different functionally defined regions of interest (ROIs), we generated 5000 streamlines that intersected each selected pair of nodes. Note that we did not perform fiber tracking between all pairs of activation nodes because 1) some were potentially subserved by short U fibers instead of association pathways, 2) some were anatomically implausible, and 3) fiber tracking between functionally defined ROIs was computationally demanding; therefore, we had to restrain our analysis based on computational resources. For the segmentation of the major associative white matter fiber bundles (AF, SLF, FAT, ILF, UF, IFOF, emC, and MdLF), we used the White Matter Query Language (Wassermann et al., 2016) to quickly filter streamlines from each subject's whole-brain probabilistic tractography (1 000 000 streamlines generated). The white matter query language allows the reliable extraction of these major associative white matter fiber bundles across subjects without manually specifying the ROIs. It is only required to determine allowed endpoints and prohibited waypoints using Freesurfer's gray and white matter parcellation labels. The latter procedure was inspired by Boukadi et al. (2019) and Wassermann et al. (2016), and we refer the reader to their articles for more details on this major associative white matter bundle segmentation procedure. All of the

functionally defined tracks and major associative fiber bundles were cleaned to remove outlier streamlines using outlier rejection algorithms from the SCILPY toolbox (https://github.com/scilus/scilpy.git) (Garyfallidis, Côté, Rheault, & Descoteaux, 2016; Garyfallidis, Brett, Correia, Williams, & Nimmo-Smith, 2012). Finally, all functionally defined tracks and major associative white matter fiber bundles were warped and concatenated in the Montréal Neurological Institute (MNI) standard space using Advanced Normalization Tools (ANTs) (http://stnava.github.io/ANTs/) and the SCILPY toolbox for topographical analysis (Avants, Tustison, & Song, 2011). All tracts were transformed into track density images (TDI) thresholded at 5% and binarized them to perform overlap analysis (Calamante, Tournier, Jackson, & Connelly, 2010). For the MdLF TDI, we used a lower threshold (2%) because the 5% initial threshold was stringent and removed most of the anterior portion of the MdLF. The latter was necessary to preserve a realistic representation of the MdLF because its density sharply decreases as it progresses towards the anterior temporal lobe.

2.3.6. Functionally defined tracks relative topography

We calculated the percentage of overlap between functionally defined tracks and segmented major associative white matter bundles (AF, SLF, FAT, ILF, UF, IFOF, emC, and MdLF). The percentage of overlap was calculated as follows: the number of voxels of the functionally defined white matter tracks overlapping the segmented major fiber bundles divided by the total number of voxels of the functionally defined white matter track multiplied by 100. We also divided all functionally defined white matter tracks and major associative white matter bundles into anterior/posterior subsections based on the anatomical landmark of the central sulcus. The latter allowed a fine-grained assessment of the percentage of overlap over the anterior/posterior axis.

3. RESULTS

3.1. Behavioral performances for the BNT

In total, five participants had to be excluded from the analysis because they had a BNT score of < 36/60 (60%) (two of these five participants were also excluded because of excessive head movements) and one because of a microphone defect during fMRI data acquisition, leading to a

final sample of 31 participants. On average, participants succeeded in naming 46.48 (± 5,84) (77%) of the BNT pictures, with reaction times of 1033.23 (±110.66) milliseconds.

3.2. fMRI results

Our voxel-wise whole-brain activation analysis (BNT > fixation cross) revealed 11 clusters of activation within the left hemisphere and eight clusters of activation within the right hemisphere. In Table 2, we report the MNI coordinates of each cluster's statistical peak of activation, anatomical label, and correspondence relative to the Brodmann cytoarchitectonic atlas.

Table 2. Clusters of activation during picture naming (BNT)

Hemisphere/lobe	Anatomical regions		MNI coordinates			T value	Cluster size
Left	**Clusters peaks**	**Brodmann**	**X**	**Y**	**Z**		**(Voxels)**
Occipital	Middle occipital gyrus (MOG)	18	-21	-93	3	16,96	1977
Temporal	Inferior temporal gyrus posterior part (pITG)	37	-48	-57	-9	14,63	690
	Superior temporal gyrus posterior part (pSTG)	22	-60	-36	6	8,76	351
	Temporal pole (TP)	36	-30	9	-30	8	78
Frontal	Inferior frontal gyrus pars orbitalis (IFGpo)	47	-36	30	-3	12,13	280
	Supplementary motor area (SMA)	6	-3	12	51	11,17	215
	Precentral gyrus (PCG)	4/3	-42	-12	36	10.29	418
Sub cortical	Posterior thalamus	N/A	-24	-30	-3	11,26	556
	Caudate nucleus	N/A	-18	-3	21	7,65	35
Cerebellum	Cerebellar crus II / VII	N/A	-9	-78	-39	10,51	761
Right	**Clusters peaks**	**Brodmann**	**X**	**Y**	**Z**		**(Voxels)**
Occipital	Middle occipital gyrus (MOG)	18	30	-90	3	16,23	1830
Temporal	Fusiform gyrus posterior part (FUGp)	37	42	-48	-15	12,12	966
	Fusiform gyrus anterior part (FUGa)	20	36	-6	-33	8,87	65
Frontal	Precentral gyrus (PCG)	4	48	-6	33	12,05	497
	Inferior frontal gyrus pars orbitalis/insula (IFGpo)	47	33	27	-3	11,19	178
	Supplementary motor area (SMA)	6	3	9	66	10,16	196
Sub cortical	Posterior thalamus	N/A	21	-30	-3	13,17	672
Cerebellum	Cerebellar crus II / VII	N/A	9	-75	-36	7,53	850

Note that the MNI coordinates also correspond to the center of Functionally defined ROIs used for fiber tracking

3.3. Fiber tracking

We performed fiber tracking within the left hemisphere between 11 pairs of functionally derived cortical regions of interest (ROIs), based on what is currently known about the associative pathways subserving the language network. Table 3 reports the results from the 11 pairs of ROIs used for planned fiber tracking, the total number of streamlines, and average track length. Note that we divided the tracks that connected the ITG and STG with the IFGpo in the dorsal and ventral parts to better study their overlap with the major associative white matter bundles.

Table 3. Functionally define white matter tracks characteristics

Functional track	Number of streamlines	Mean Length in mm (SD)	Reproducibility across participants
MOG ⇄ IFGpo	223	179.4 (± 10.7)	31,0 %
MOG ⇄ TP	2534	149.5 (± 10.4)	96,6 %
ITG ⇄ IFGpo (dorsal)	319	162.5 (± 8.9)	96,6 %
ITG ⇄ IFGpo (ventral)	1405	135.0 (± 10.4)	96,6 %
ITG ⇄ TP	3738	102.0 (± 10.7)	96,6 %
STG ⇄ TP	3153	98.5 (± 9.9)	100 %
STG ⇄ IFGpo (dorsal)	885	152.4 (± 11.1)	96,6 %
STG ⇄ IFGpo (ventral)	1723	132.4 (± 13.8)	96,6 %
IFGpo ⇄ SMA	1004	91.0 (± 4.4)	89,7 %
IFGpo ⇄ TP	2213	89.1 (± 10.1)	96,6 %
SMA ⇄ PCG	1182	64.0 (± 6.9)	93,1 %

From the whole-brain tractography, we extracted the major associative white matter bundles that were potentially associated with the ventral and dorsal streams of language. We segmented the ILF, UF, IFOF, emC, and MdLF for the ventral stream and the AF, SLF-I, SLF-II, SLF-III, and FAT for the dorsal stream. Table 4 reports the total number of streamlines, average length, and reproducibility across participants of the major associative white matter fiber bundles.

Table 4. Major associative white matter fiber bundles characteristics

Associative bundles	Number of streamlines	Mean Length in mm (SD)	Reproducibility across participants
AF	10000	124.5 (± 15.9)	100 %
SLF-I	13456	85.5 (± 18.0)	100 %
SLF-II	4495	78.3 (± 17.9)	100 %
SLF-III	27988	121.0 (± 17.3)	100 %
FAT	34809	81.9 (± 8.7)	100 %
MdLF	43783	90.9 (± 19.6)	100 %
IFOF	4640	173.9 (± 22.5)	100 %
emC	1521	187.0 (± 13.2)	100 %
ILF	3902	120.5 (± 17.5)	100 %
UF	13151	88.5 (± 19.8)	100 %

3.4. Functionally defined white matter tracks overlap with major associative white matter bundles

In general, there was considerable overlap between the functionally defined white matter tracks and segmented major associative white matter bundles. To interpret an overlap as meaningful, we used the following two criteria: **1)** the overlap is > 25% and **2)** the major associative white matter bundles share starting and ending points (according to the anatomical literature) with the functionally defined white matter. All overlap percentages are reported in Table 5 and Figure 5 shows the topographical organization of these functionally defended white matter tracks and their overlap with the major associative white matter bundles. We will first address the functionally defined white matter track that runs along the ventral pathway, followed by the dorsal pathway.

3.5. Ventral white matter bundles

3.5.1. Functionally defined tracks along the ILF

The ITG ⇄ TP (38%) and the MOG ⇄ TP (28.4%) both had meaningful overlap with the ILF. However, they also showed considerable overlap with IFOF (see Table 6). Topographically, they both run along the most dorsal part of the ILF and the ventral part of the IFOF (except for their anterior end, which dives in the anterior temporal lobe) (see Figure 5). Note that there was considerable overlap between the MOG ⇄ TP and the IFOF (53.8%). However, the IFOF does not have termination points on the TP. Furthermore, the IFOF is known to overlap substantially with the ILF (Catani & de Schotten, 2012) (see Supplementary Table 2 and Figure 5 for further details).

3.5.2. Functionally defined tracks along the IFOF

The ventral part of the ITG ⇄ IFGpo (61.9%) and the MOG ⇄ IFGpo (56.8%) both had meaningful overlap with the IFOF. Topographically speaking, they both follow the course of the IFOF for most of their part and show some local segregation near both extremities (see Figure 5).

3.5.3. Functionally defined track along with the emC

The ventral STG ⇄ IFGpo had a meaningful overlap with the emC (51.7%). The STG ⇄ IFGpo track lies within emC for most of its body. This shows that some local segregation nears both ends (see Figure 5). Note that we did not retain the ITG ⇄ IFGpo (ventral) as a part of the emC even if the overlap was high (52.6%) because it didn't meet criterion #2 to be considered a meaningful overlap.

3.5.4. Functionally defined track along the MdLF

The STG ⇄ TP had a meaningful overlap with the MdLF (47,4%) and is organized along its anterior/posterior axis for most of its trajectory, but the amount of overlap is reduced in the most anterior part of the temporal lobe (see Figure 5). A finer-grained analysis, where we divided the track in a posterior/anterior subsection based on the anatomical landmark of the central sulcus, showed that the posterior part of the STG ⇄ TP had 93.2% overlap with the MdLF, while its anterior part had 27.1% (see Supplementary Tables 3 and 4).

3.5.5. Functionally defined track along with the UF

The IFGpo ⇄ TP had a meaningful overlap of 52.7% with the UF. The overlap is evident from the temporal lobe to the level of the anterior insula, and then the extremities become relatively segregated (see Figure 5).

3.6. Dorsal white matter bundles

3.6.1. Functionally defined tracks along with the AF

The dorsal parts of the ITG ⇄ IFGpo (57.7%) and the STG ⇄ IFGpo (42.5%) both had meaningful overlap with the AF. (see table 6). Furthermore, their global trajectories were highly similar and shared as much as 52,6% of their voxels (see Supplementary Table 1). Both arched around the Sylvian fissure following the course of the AF and reached the inferior frontal gyrus (see Figure 5).

3.6.2. Functionally defined tracks along with the FAT

The SMA ⇄ PCG (46.1%) and the IFGpo ⇄ SMA (29.3%) both had meaningful overlap with the FAT. (see table 6). The SMA ⇄ PCG intersects the FAT, and its fibers originating from the SMA are located more ventromedially than the dissected FAT. Similarly, the SMA ⇄ PCG fiber that reaches the PCG was located slightly dorsally with respect to the most ventral part of the FAT near the IFG. The IFGpo ⇄ SMA walked along the medial wall of the FAT for most of its parts (see Figure 5).

3.7. Functionally defined tracks reproducibility

Almost all functionally defined tracks had a high level of reproducibility (> 85%) across 31 participants. However, the MOG ⇄ IFGpo had a low reproducibility level of 31% (see table 4 for more details).

Table 5. Percentage of overlap between functionally defined white matter track and major associative white matter bundles

	ILF	UF	IFOF	emC	MdLF	AF	SLF-I	SLF-II	SLF-II	FAT
ITG ⇄ TP	38,0	13,7	34,9	21,3	17,7	11,2	0,0	0,0	0,0	0,0
MOG ⇄ TP	28,4	10,3	53,8	24,2	12,0	2,1	0,0	0,0	0,0	0,0
ITG ⇄ IFGpo (ventral)	25,0	17,4	61,9	52,6	13,5	9,4	0,0	0,0	0,0	0,0
MOG ⇄ IFGpo	17,4	10,6	56,8	38,4	13,4	4,2	0,0	0,0	0,0	0,0
STG ⇄ IFGpo (ventral)	1,7	16,4	41,5	51,7	40,1	7,5	0,0	0,0	0,0	0,0
STG ⇄ TP	5,7	17,9	19,5	24,8	47,4	6,5	0,0	0,0	0,0	0,0
IFGpo ⇄ TP	0,1	52,7	39,2	40,1	0,0	0,0	0,0	0,0	0,0	0,0
ITG ⇄ IFGpo (dorsal)	0,6	0,7	3,5	9,2	17,9	57,7	0,4	10,7	13,4	15,9
STG ⇄ IFGpo (dorsal)	0,0	0,5	2,1	6,6	27,9	42,5	0,0	1,2	10,4	17,6
SMA ⇄ PCG	0,0	0,0	0,0	0,0	0,0	6,4	2,5	13,3	0,1	46,1
IFGpo ⇄ SMA	0,0	0,4	1,8	3,0	0,0	4,5	0,4	0,2	1,2	29,3

The percentage represents the overlap of the functionally defined white matter track identified in the left column over the major associative white matter bundles identified in the top row. Highlighted data are the ones considered to be a "meaningful overlap" and presented in the text.

3.8. Overlap between the different functionally defined white matter track

Most of the functionally defined white matter tracks that shared endpoints expressed considerable overlap (>25%) when compared to those that did not share endpoints. The reader is referred to Supplementary Table 1 for further information on the percentage of overlap between different functionally defined white matter tracks.

3.9. Overlap between the different major associative white matter bundles

Seven out of ten major associative white matter bundles showed considerable (>25%) overlap. The latter is expected because a few major associative white matter bundles tend to share similar trajectories but different ending points. The general tendency is that ventral pathways express overlap with each other, whereas dorsal ones express overlap with each other as well. However, they do not systematically overlap, and the majority of their volume (> 50%) is segregated from other ones in all cases (except the UF). The reader is referred to Supplementary Table 2 for further information on the percentage of overlap between different major associative white matter bundles.

4. DISCUSSION:

4.1. Towards a neurocognitive model of picture naming

We investigated the functional network involved in picture naming and reconstructed the dorsal and ventral connections that underlie this network. We quantified the amount of overlap between the functionally defined white matter track and the major associative white matter bundles to estimate the most probable pathway interconnecting the two activated brain regions.

The mean BNT performance level was relatively low (46.48/60) compared to the neuropsychological normative data (Roberts & Doucet, 2011; Strauss et al., 2006). However, one must remain cognizant that the BNT administration procedure was atypical because it was adapted to the fMRI acquisition protocol (participants only had three seconds to name each picture within a noisy MRI apparatus). It is well documented that behavioral performances in an fMRI environment is generally worse than those in standard testing conditions (Gutchess & Park, 2006). However, our fMRI findings are generally in agreement with the results from studies that investigated picture naming in healthy subjects and patients.

4.1.1. A ventral pathway for picture naming

Our results show that a ventral pathway that "maps image and sound to meaning" (to borrow Hickok and Poeppel, 2004 words) is formed by interconnecting the MOG, ITG, STG with the TP and IFGpo via the IFOF, ILF MDLF, emC, and UF.

More specifically, we showed that the MOG and ITG were connected to IFGpo by the IFOF, forming a direct lexicosemantic pathway. In the context of picture naming, the MOG and ITG are thought to be involved in perceptual processing, whereas the IFGpo is thought to be involved in the retrieval of semantic concepts and words (Price, 2012; Price et al., 2005). We do not exclude that the ITG drives modality-specific conceptual knowledge, as proposed by grounded cognition theory (Patterson & Lambon Ralph, 2016; Pulvermüller, 2013). This makes sense, knowing that direct electrical stimulation of the IFOF during picture naming systematically induces semantic paraphasias (De Witt Hamer et al., 2011; Duffau, Moritz-Gasser, et al., 2013; Sarubbo et al., 2015). One could question why our peak activation within the IFG was localized within the pars orbitalis (BA 47) and not in the famous territory of Broca (IFG pars opercularis and triangularis, or BA

44/45). This result appears to make a lot of sense when we consider that the IFGpo functional activity is associated with controlled access (i.e., top-down processing) to stored conceptual representations, while BA44/45 is more related to the selection of candidates between distracting or competing for information (see Badre and Wagner, 2007 for a review). On a different note, we showed that the MOG ⇄ IFGpo connection was only reproduced in 31% of the sample, which cast doubt on its implication in the context of picture naming. We think it is more plausible that short-distance connections first connect the MOG to the ITG, and then the ITG communicates with the IFGpo via the IFOF. Otherwise, this would imply that direct stimulation of the IFOF could produce visual errors during picture naming (the kind of error observed in apperceptive visual agnosia). To our knowledge, this has not been reported in scientific literature.

The STG was connected to the IFGpo by emC. Based on Saur et al. (2008) and Price (2012), we extrapolated that this sub-network could be useful for performing semantic retrieval based on the auditory representation of words. However, it is not clear how we access auditory representations of words in picture naming. Is it the ITG that first allows picture recognition to communicate (or spread its activity in a bottom-up fashion) to the STG via short-distance U-shaped fibers or the MdLF? Is it IFGpo that seeks the auditory representation of words within the STG in a top-down fashion via the emC? Or could it be both? However, this remains to be investigated using other methods (i.e., functional connectivity analysis). However, part of the answer may reside in the "two-step process of controlled semantic processing" proposed by Badre et al., where the IFGpo drives the controlled retrieval of conceptual knowledge by influencing activation in crossmodal and modal conceptual stores (Badre & Wagner, 2007). Before closing on the topic of emC, let us emphasize that the term emC can be misleading because it conflates two concepts: **1)** the idea of the extreme capsule as a location in space between the insula and claustrum through which fiber bundles may pass, and **2)** a ventral frontotemporal fasciculus. Classically, the term "capsule" was reserved to designate a neuroanatomical landmark (i.e., internal capsule or external capsule) where multiple white matter tracts pass more than a specific tract per se (please see Axer et al., 2013; Bajada et al., 2015; Duffau et al., 2013a; Shekari et al., 2021 for further discussion related to this topic). An alternative proposition could be the superficial or dorsal layer of the IFOF, as described by Sarubbo et al. (2013). Still, we chose to keep

the emC in this article to remain faithful to its original name, as there is no other commonly accepted terminology or consensus in the field to designate this frontotemporal fasciculus.

MdLF also appears to bind a great deal of information together in the temporal lobe by interconnecting the STG, ITG, and TP, forming a rich semantic network. This idea is supported by cases of pure anomia during picture naming when direct electrical stimulation was applied at the level of the posterior part of the MdLF (Sarubbo et al., 2015).

In addition to the previously addressed ventral pathway connection, our results support the idea of an indirect route connecting the MOG and ITG to the IFGpo passing through the TP. This pathway, formed by the combination of the ILF and UF, is thought to act as an "add on" route that could be involved in word-finding for most difficult items such as unique entities (Papagno, 2011). As proposed by Duffau et al. (2009) and Mandonnet et al. (2007), this indirect route may not be essential for picture naming. Further investigation should be conducted to verify whether this pathway forms a subnetwork specialized in unique semantic entities (i.e., famous faces and proper names).

We were surprised by the absence of significant activation within the inferior parietal lobule (especially the angular gyrus), which is frequently associated with semantic processing (Bonner, Peelle, Cook, & Grossman, 2013; Price et al., 2005). However, evidence suggests that the angular gyrus is often recruited during tasks that require reading or auditory analysis of speech (i.e., lexical decision tasks and sentence comprehension) (Bonner et al., 2013; Price, 2012; Saur et al., 2008a). Furthermore, Price et al. (2005) showed that the angular gyrus was active when they asked participants to perform a semantic judgment about images (i.e., is this image a living thing?). In other instances, picture naming does not activate the angular gyrus.

In summary, the brain activation that we reported in the ventral pathway and its underlying connections is consistent with the clinical literature. First, Brambati et al. (2006) investigated 152 participants with or without various neurodegenerative diseases and showed that general picture-naming performance was positively associated with gray matter volumes in the bilateral posterior inferior temporal cortex, anterior fusiform, left temporal pole, middle temporal gyrus, and hippocampal complex. Similarly, using voxel-based lesion-symptom mapping (VLSM) in 96

left-hemisphere stroke survivors, Baldo et al. (2013) concluded that the performance of the Boston Naming Test (BNT) was associated with the whole (anterior to posterior) left middle and superior temporal gyrus and inferior parietal lobule (angular and supramarginal gyri). They also indicated that the left mid-posterior middle temporal gyrus and its underlying white matter appear to be highly related to lexical-semantic retrieval of the BNT items. The latter finding is interesting because it highlights the potential implication of white matter as a key factor in binding the activity of different nodes of gray matter that constitute the network of picture naming. Similarly, Xing et al. (2018) showed that the integrity of the ventral stream tracks connecting the left STG or inferior parietal lobule with the left IFG is positively related to semantic processing.

4.1.2. A dorsal pathway for picture naming

Our results show that a dorsal pathway that "maps sound to speech" (to cite again Hickok and Poeppel, 2004) is formed by interconnecting the ITG, STG, IFGpo, PCG, and SMA via the AF and the FAT. More specifically, we showed that the ITG and STG were also connected to the IFGpo by AF. The latter sub-network is thought to be mainly involved in phonological processing because direct electrical stimulation of the AF is known to cause phonemic paraphasia during picture naming (Duffau et al., 2003; Duffau, Moritz-Gasser, et al., 2013; Maldonado, Moritz-Gasser, De Champfleur, et al., 2011; Maldonado, Moritz-Gasser, & Duffau, 2011; Sarubbo et al., 2015). Furthermore, the STG and ventrolateral prefrontal cortex are known to be active during verbal tasks that require phonological processing (i.e., sublexical pseudoword repetition) as well as in picture-based phonological judgment tasks (i.e., the object has two syllables) (Price et al., 2005; Saur et al., 2008). To support this idea, microstructural changes within the AF have also been documented in lv-PPA and nv-PPA (Galantucci et al., 2011).

However, an important question arises considering that we found ventral but also a dorsal connection between the posterior STG, ITG, and the IFGpo: "How is it that the posterior STG and ITG seem to contribute/connect to both, yet independent, neuro-cognitive systems (namely the dorsal and ventral pathway of language)?" The first part of the answer may be found in DeWitt and Rauschecker (2013). They highlighted that the STG (BA 22 or "Wernicke's area") is involved in both ventral and dorsal auditory streams by analyzing data from comparative animal studies,

healthy humans, and patients. More importantly, they suggest that the anterior part of the Wernicke area contributes to the ventral stream (i.e., an auditory word from the area), whereas its posterior part is more devoted to the dorsal stream (i.e., inner speech area) (DeWitt & Rauschecker, 2013). The answer concerning the ITG is less clear but finds some echoes in Vigneau et al.'s study 2006 meta-analysis. In their study, they investigated the activation peaks in the left hemisphere from 129 studies using a spatial clustering algorithm. The results showed that phonological and semantic clusters showed significant overlap at the level of the posterior inferior temporal gyrus. Interestingly, the MNI coordinates are highly similar to those reported in the present report. According to the authors, this brain territory devoted to visual material includes a sub-region (T3p in their article) that might act as an " interface between phonological and semantic processes for audiovisual processing" (Vigneau et al., 2006). The latter interpretation is interesting, especially when we consider visual input (i.e., written text and objects/pictures). However, it is reasonable to think that the posterior ITG "feeds" the dorsal pathway in a bottom-up fashion, while not being a unit of phonological processing per se. Furthermore, the posterior ITG is not known to be activated during phonological tasks involving auditory-verbal input (i.e., sublexical pseudoword repetition) (Price, 2012; Saur et al., 2008b)

We also demonstrated direct structural connections between IFGpo, PGC, and SMA via FAT. We think that these connections are related to speech production during picture naming. Evidence from the PET and fMRI literature suggests that SMA activity is involved in the planning of motor movement execution during speech production (Price, 2012). Direct electrical stimulation of this region during awake brain surgery leads to vocalization, speech interference, or speech arrest (Penfield 1959). We believe that the activity detected at the level of the precentral gyrus is related to the orofacial movement involved in speech production. This activity cluster is located ventrolaterally in the precentral gyrus, which roughly corresponds to the somatotopic representation of effectors related to speech (face, mouth, jaw, lips, etc.). Again, this is well supported by PET/fMRI literature and direct electrical stimulation studies (Penfield & Rasmussen, 1950; Price, 2012). Our data add to the idea that FAT could be involved in speech initiation, as reported by Dick et al. (2019) and Duffau (2016).

4.1.3. Other cortical and sub-cortical brain activations

Considering that the presented stimuli were drawings, it is no surprise that we detected significant activation in posterior brain regions related to various levels of visual/perceptual processing (posterior thalamus, middle occipital gyrus, and posterior part of the inferior temporal gyrus). Activation in the occipital cortex is thought to be associated with early visual processing (Hubel and Wiesel, 2004), and activity detected in the posterior inferior temporal gyrus is also assumed to be related to visual object recognition (Grill-spector, Kourtzi, & Kanwisher, 2001; Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999). Although the spatial resolution of fMRI is limited when it comes to spatial inferences in smaller subcortical nuclei, we think that posterior thalamic activation could correspond to activation in the lateral geniculate nucleus (LGN), which is well known to be involved in early visual processes. However, these thalamic activations could also be driven by the pulvinar nucleus (one does not exclude the other). In this context, evidence suggests that the thalamus might play a critical role in maintaining an optimal level of arousal in specific cortical networks during task execution (Llano, 2016). Moreover, evidence from deep brain stimulation studies and thalamic stroke patients has shown that thalamic nuclei (i.e., pulvinar, posterior, and mid ventrolateral nuclei) are involved in lexical access (De Witte et al., 2011; Hebb & Ojemann, 2013).

We believe that left caudate activation during picture naming represents motor articulation processes since the involvement of the striatum is well known in the realm of the motor network. However, it is also possible that striatal activity reflects an executive component because it has been reported that direct electrical stimulation of the head of the caudate induces perseveration during picture naming (Duffau, Moritz-Gasser, et al., 2013).

Significant cerebellar activity in a sparse cluster extending from crus-II and crus-VII was also observed. Classically, cerebellar activation has consistently been linked to motor function. This idea is still well supported by neuroimaging and patient studies (i.e., posterior fossa syndrome), which presents with ataxic dysarthria (Ackermann & Brendel, 2016; Price, 2012). However, such a simplistic conclusion should be avoided because the study of the functional role of the cerebellum is still an emerging field, and many studies suggest that its role is more complex than initially thought (Fiez, 2016; Schmahmann, 2010). In fact, in her review, Price (2012) highlights

that the cerebellum could be involved in speech production as well as during word retrieval for speech production.

5. LIMITATIONS:

This article is among the first to investigate and present a unified view of the implications of gray and white matter in a neuropsychological test that assesses picture naming in a healthy adult population. Future studies including more subjects and/or more updated acquisition sequences (i.e., multishell, higher b-values) could help to support the present results.

6. CONCLUSION:

Our results are concordant with multiple white matter anatomical studies and fMRI meta-analyses, which brings us strong confidence in them. It also supports the dual-stream model of language and further encourages the idea that the ITG and STG may have pivotal roles within this model. Finally, this article represents a useful source of knowledge for clinicians and researchers, as it synthesizes and fills the gap between data obtained using various methods (MRI, post-mortem dissection, comparative animal studies, and intraoperative direct electrical stimulation) and from different populations (patients and healthy subjects).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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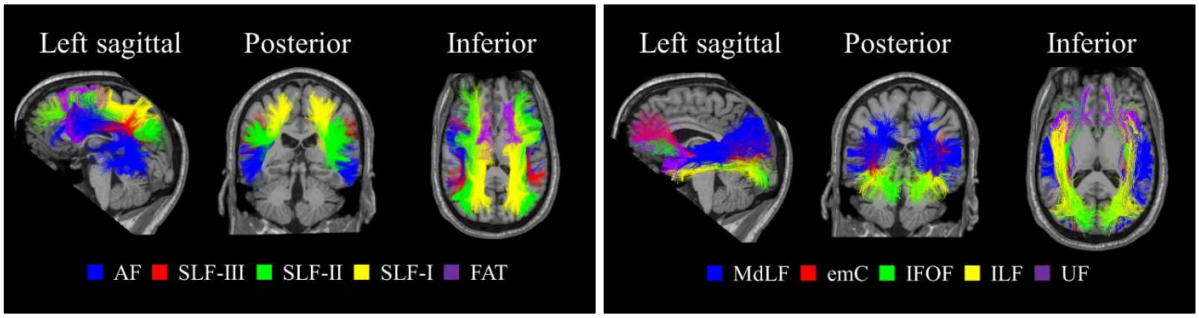
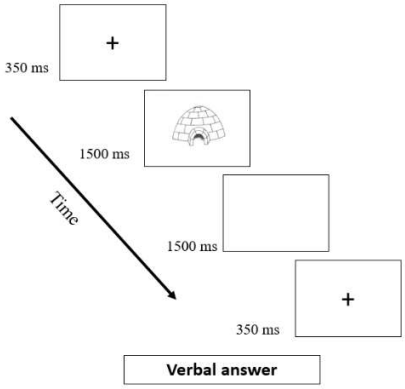
Figures and references

Figure 3. – In-vivo segmentation example of ventral and dorsal major associative white matter bundles.



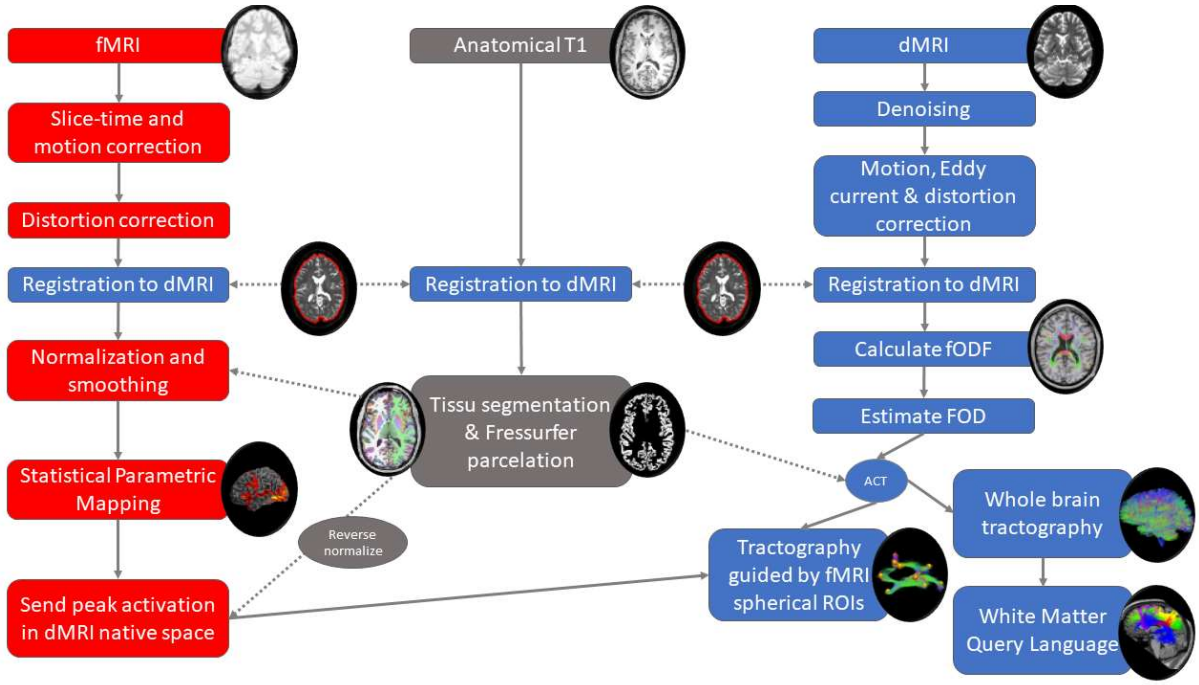
Left panel: Segmentation of the dorsal white matter fiber bundles. Right Panel: segmentation of the ventral white matter fiber

Figure 4. – Example of a BNT trial.



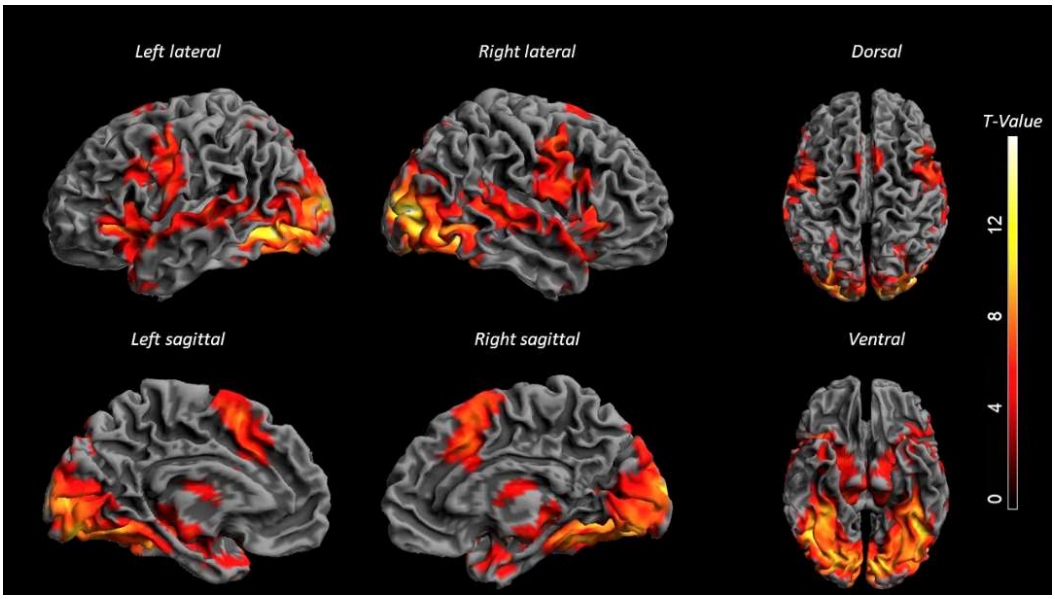
As soon as the picture appeared on the screen, the participants had a total of 3 seconds to name the picture verbally with a single word.

Figure 5. – Scheme of the MRI data pre and post processing steps.



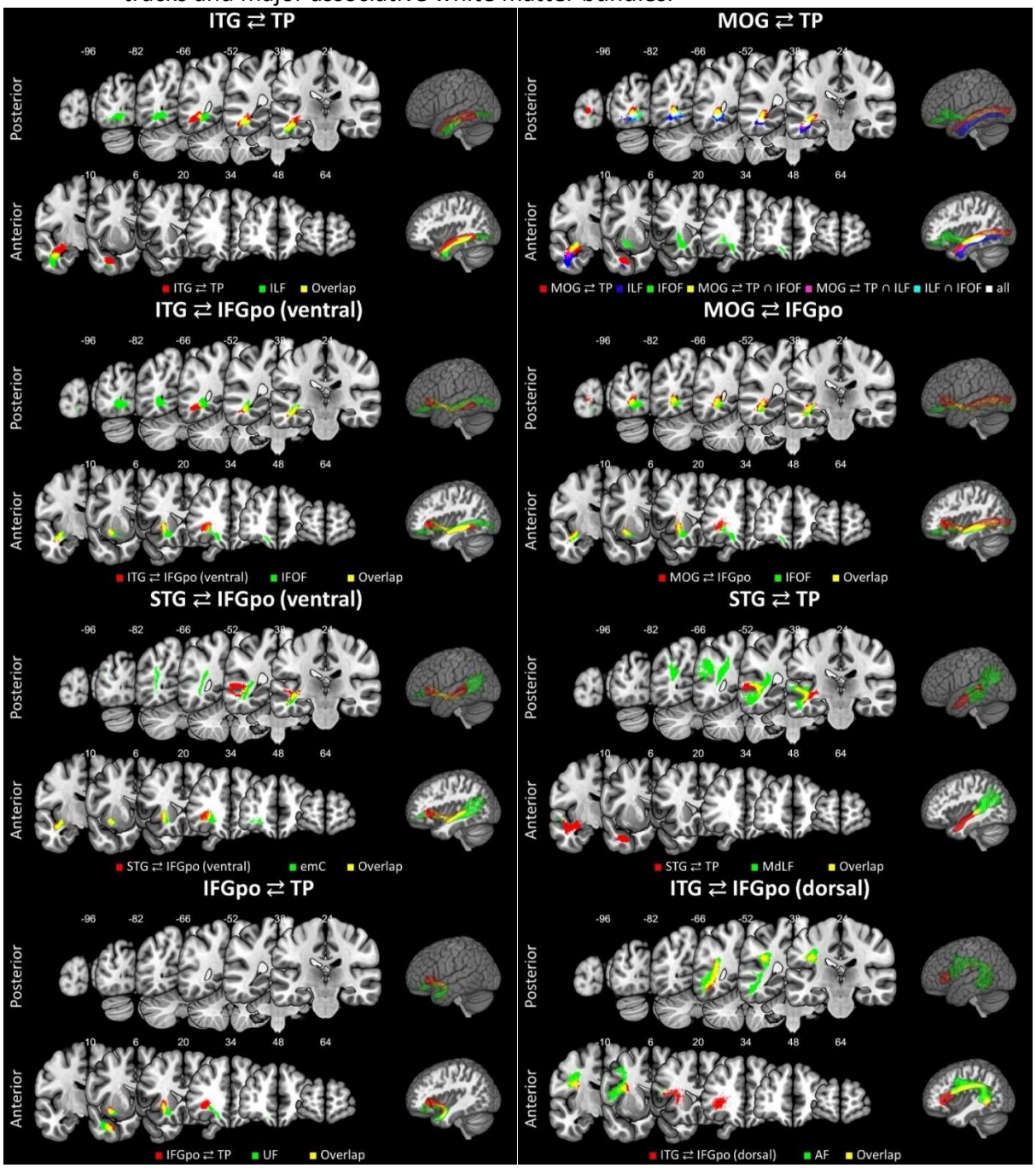
List of abbreviations in the figure: Anatomically Constrained Tractography (ACT), Regions Of Interests (ROIs), fiber orientation distribution function (fODF), fibre orientation distribution (FOD).

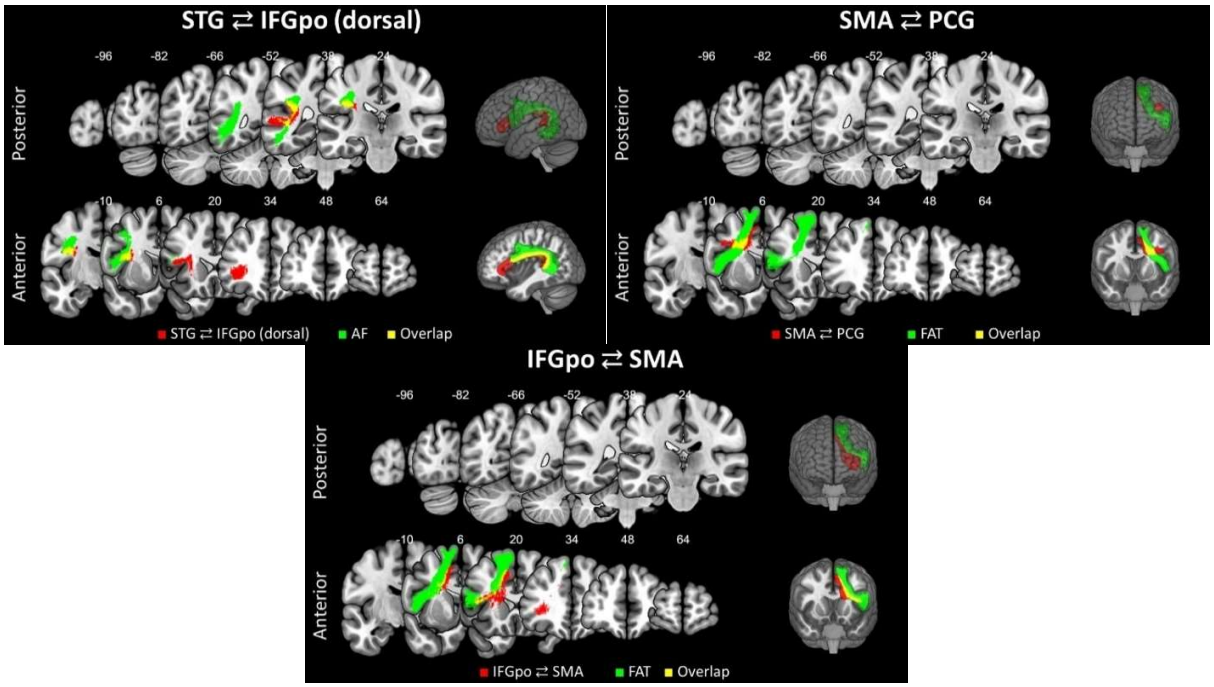
Figure 6. – Brain activation during the execution of the BNT



projected on a cortical surface ($p < 0.05$ [FWE], $K \geq 30$)

Figure 7. – Spatial distribution of the overlap pattern between functionally defined white matter tracks and major associative white matter bundles.





Each panel displays white matter tracks binary map overlaid onto the meaningful (or most related) major associative white matter bundles.

Supplementary material:

Supplementary table 1 -: Percentage of overlap between the different functionally defined white matter tracks

	MOG ⇄ IFGpo	MOG ⇄ TP	ITG ⇄ IFGpo (dorsal)	ITG ⇄ IFGpo (ventral)	ITG ⇄ TP	STG ⇄ TP	STG ⇄ IFGpo (dorsal)	STG ⇄ IFGpo (ventral)	IFGpo ⇄ SMA	IFGpo ⇄ TP	SMA ⇄ PCG
MOG ⇄ IFGpo	100,0	54,8	12,1	35,3	20,2	15,2	10,2	33,4	8,3	19,5	0,0
MOG ⇄ TP	48,8	100,0	1,6	21,4	48,4	34,3	0,0	12,3	0,0	7,9	0,0
ITG ⇄ IFGpo (dorsal)	12,0	1,7	100,0	13,8	7,2	0,0	52,6	9,6	22,6	8,7	0,1
ITG ⇄ IFGpo (ventral)	60,1	40,8	23,8	100,0	55,4	17,4	15,0	50,9	11,6	35,2	0,0
ITG ⇄ TP	25,0	67,3	9,1	40,3	100,0	36,8	0,0	8,8	0,0	10,3	0,0
STG ⇄ TP	19,5	49,3	0,0	13,1	38,0	100,0	13,7	42,4	0,0	11,5	0,0
STG ⇄ IFGpo (dorsal)	9,5	0,0	49,4	8,2	0,0	9,9	100,0	17,2	24,7	8,5	0,1
STG ⇄ IFGpo (ventral)	52,6	21,8	15,3	47,2	11,2	52,2	29,2	100,0	12,2	34,4	0,0
IFGpo ⇄ SMA	9,6	0,0	26,5	7,9	0,0	0,0	30,7	8,9	100,0	8,1	16,4
IFGpo ⇄ TP	54,7	24,8	24,7	58,0	23,2	25,1	25,6	61,1	19,7	100,0	0,0
SMA ⇄ PCG	0,0	0,0	0,3	0,0	0,0	0,0	0,4	0,0	47,5	0,0	100,0

The percentage represent the overlap of the functional track identified in the left column over the functional track identified in the top row.

Supplementary table 2 -: Percentage of overlap between the different major associative white matter bundles

	AF	SLF-I	SLF-II	SLF-III	FAT	MdLF	IFOF	emC	ILF	UF
AF	100,0	5,9	21,8	19,5	17,5	31,9	0,6	6,0	0,7	0,0
SLF-I	6,2	100,0	24,5	0,0	7,9	3,0	0,0	0,0	0,0	0,0
SLF-II	20,3	21,8	100,0	2,3	7,8	29,6	0,0	2,6	0,0	0,0
SLF-III	42,3	0,1	5,4	100,0	31,3	7,1	0,0	0,1	0,0	0,0
FAT	18,4	8,0	8,8	15,2	100,0	0,0	0,0	0,0	0,0	0,0
MdLF	12,1	1,1	12,1	1,2	0,0	100,0	1,6	7,7	1,9	0,0
IFOF	1,0	0,0	0,0	0,0	0,0	6,9	100,0	36,8	28,3	21,8
emC	11,8	0,0	5,6	0,0	0,0	43,5	44,3	100,0	7,1	16,3
ILF	1,4	0,0	0,0	0,0	0,0	10,5	35,7	7,4	100,0	0,9
UF	0,0	0,0	0,0	0,0	0,0	0,0	51,6	32,1	1,6	100,0

The percentage represent the overlap of the associative white matter bundles identified in the left column over the ones identified in the top row.

Supplementary table 3 -: Percentage of overlap between the anterior part of functionally defined white matter track and the anterior part of major associative white matter bundles

	AF	SLF-I	SLF-II	SLF-III	FAT	MdLF	IFOF	emC	ILF	UF
MOG ⇄ IFGpo	0,1	0,0	0,0	0,0	0,1	9,3	55,6	59,1	5,6	23,6
MOG ⇄ TP	0,0	0,0	0,0	0,0	0,0	11,2	35,3	29,2	22,1	23,5
ITG ⇄ IFGpo (dorsal)	41,4	0,5	6,8	15,7	24,9	0,0	3,7	5,9	0,0	1,1
ITG ⇄ IFGpo (ventral)	0,1	0,0	0,0	0,0	0,0	5,4	69,5	66,6	12,2	26,9
ITG ⇄ TP	0,0	0,0	0,0	0,0	0,0	9,6	29,7	21,3	33,9	23,8
STG ⇄ IFGpo (dorsal)	37,2	0,0	1,5	14,0	27,4	0,0	3,3	5,2	0,0	0,8
STG ⇄ IFGpo (ventral)	0,1	0,0	0,0	0,0	0,0	16,5	56,2	64,9	2,3	23,4
STG ⇄ TP	0,0	0,0	0,0	0,0	0,0	27,1	24,5	25,4	7,8	25,8

The percentage represent the overlap of the anterior part of functionally defined white matter track identified in the left column over the anterior part of major associative white matter bundles identified in the top row. For this analysis, the functionally defined white matter track and major associative white matter bundles were divided in a posterior/anterior subsection based on the anatomical landmark of the central sulcus

Supplementary table 4 -: Percentage of overlap between the posterior part of functionally defined white matter track and the posterior part of major associative white matter bundles

	AF	SLF-I	SLF-II	SLF-III	FAT	MdLF	IFOF	emC	ILF	UF
MOG ⇄ IFGpo	7,5	0,0	0,0	0,0	0,0	16,7	57,8	21,7	26,9	0,0
MOG ⇄ TP	3,7	0,0	0,0	0,0	0,0	12,7	68,2	20,3	33,3	0,0
ITG ⇄ IFGpo (dorsal)	86,6	0,3	17,6	9,2	0,0	49,4	3,2	15,1	1,7	0,0
ITG ⇄ IFGpo (ventral)	26,7	0,0	0,0	0,0	0,0	28,3	47,9	26,8	48,7	0,0
ITG ⇄ TP	26,4	0,0	0,0	0,0	0,0	28,6	41,8	21,4	43,5	0,0
STG ⇄ IFGpo (dorsal)	51,9	0,0	0,8	4,0	0,0	77,6	0,0	9,1	0,0	0,0
STG ⇄ IFGpo (ventral)	25,0	0,0	0,0	0,0	0,0	95,6	6,9	20,5	0,5	0,0
STG ⇄ TP	21,3	0,0	0,0	0,0	0,0	93,2	8,2	23,4	1,1	0,0

The percentage represent the overlap of the posterior part of functionally defined white matter track identified in the left column over the posterior part of major associative white matter bundles identified in the top row. For this analysis, the functionally defined white matter track and major associative white matter bundles were divided in a posterior/anterior subsection based on the anatomical landmark of the central sulcus

CREDIT STATEMENT

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HIGHLIGHTS

•We integrated fMRI with tractography to map cortical and fiber bundles involved in picture naming. •This study is in agreement with the dual-stream framework of language. •Likewise, it supports the hypothesis of a ventral indirect route passing by the temporal pole. • It also suggests that the ITG and STG might play pivotal roles within the dual-stream framework.

Chapitre 3 – [Discussion générale]

6. Résumé et interprétation générale des résultats

Cette thèse est constituée de deux études. Dans un premier temps, l'étude de la portée (article #1) visait à mieux comprendre les aspects méthodologiques associés à l'intégration de l'IRMf pour guider la tractographie. En second lieu, l'étude empirique (article #2) visait à cartographier les composantes fonctionnelles et structurelles du réseau cérébral impliquées dans la dénomination d'images en intégrant l'IRMf pour guider la tractographie.

Sommairement, l'analyse critique de 80 articles ayant intégré l'IRMf pour guider la tractographie nous a d'abord permis d'effectuer 19 constats[8] qui concernent les défis méthodologiques associés à cette méthode de combinaison multimodale ainsi que de proposer certaines pistes de solution et des recommandations. Nous avons ensuite pu appliquer ces connaissances dans le cadre d'une étude empirique qui nous a permis de proposer un modèle neurocognitif de la dénomination d'images (voir figure 2 de la section 10). Dans ce modèle, nous validons la présence d'une voie ventrale et dorsale du traitement de l'information en contexte de dénomination d'images et nos données supportent aussi l'hypothèse voulant que les parties postérieures du cortex inférotemporal et du gyrus temporal supérieur puissent servir d'interface entre les deux voies du traitement de l'information. Les résultats obtenus appuient également l'idée d'une voie ventrale indirecte transigeant par le lobe temporal antérieur.

Dans le cadre de cette discussion, nous reviendrons d'abord sur les découvertes critiques des deux articles de thèse ainsi que les considérations/implications théoriques, cliniques et méthodologiques qui en découlent. Ensuite, nous aborderons les contributions originales, les avenues de recherche future ainsi que les limites des études présentées pour finalement conclure.

[8] En référence aux 19 « findings » de l'article #1 de cette thèse

6.1 Article #1 étude de la portée

Via un examen de la portée (scoping review), cet article a permis la recension et l'analyse critique de 80 études publiées entre 1999 et 2021. Nous y proposons notamment 19 constats qui permettent de mieux orienter la communauté scientifique dans l'application de cette méthode intégrative des données multimodales. Les constats les plus importants que nous résumerons ci-bas visent à améliorer la qualité méthodologique des futures études en faisant la promotion des meilleures pratiques en plus d'offrir des pistes de solutions aux défis inhérents à l'intégration de l'IRMf pour guider la tractographie.

Parmi les points méthodologiques pouvant être améliorés dans ce type d'études, nous relevons d'abord que les petites tailles d'échantillon en IRMf demeurent fréquentes diminuant ainsi le potentiel de reproductibilité des résultats. Ainsi, on pourrait considérer la possibilité d'avoir recours à des bases de données à plus grand effectif (ex. Human Connectome Project) ou encore, lorsque cela est possible, d'appuyer les conclusions par un processus de triangulation des données (ex. présenter de résultats similaires obtenues à l'aide de méthodologie alternatives (ex. études cliniques, études animales, études invasives, etc.). En ce qui concerne l'usage de l'IRMd, bon nombre d'articles analysés présentaient des manquements au niveau de la divulgation des paramètres de tractographie utilisés. Ceci peut donc empêcher de reproduire les études ou de collecter des données en vue d'effectuer des méta-analyses. Qui plus est, le recours à des modèles microstructurel sous-optimaux (ex. tenseur de diffusion / DTI) persiste malgré leurs rendements moindres pour effectuer la tractographie là où l'organisation de la matière blanche est considérée complexe[9]. De façon similaire, nous relevons que les stratégies visant à réduire les risques de faux positifs par l'incorporation de règles aprioriques qui empêchent la tractographie dans les régions cérébrales non plausibles[10] (ex. anatomically constrained tractography / ACT) étaient somme toute absentes. En outre, la tendance à mesurer les valeurs moyennes des propriétés microstructurelles obtenues sur l'ensemble d'un track était omniprésente au détriment du profilage tractométrique pouvant s'avérer plus sensible et informatif.

[9] c. -à d là où les fibres se croisent, s'embrassent ou s'étiolent (fanning out), ce qui représente ≈ 90% des voxels comportant de la matière blanche (Descoteaux, 2008; Jeurissen et al., 2013)
[10] Ventricules cérébraux, matière grise, espace sous-dural, etc.

Nous avons également identifié qu'il était possible d'améliorer la validité et/ou la spécificité des résultats des études analysés en adoptant trois conduites scientifiques simples **1)** lorsque cela est possible, présenter des données convergentes issues de méthodologies différentes (ce qui n'a pas été fait dans 82.5% des cas analysés), **2)** libeller les tracks obtenues en fonction de leur correspondance anatomique (ce qui n'a pas été fait pour 32,5% des études investiguées) et **3)** offrir un tract alternatif ou de comparaison (niveau de base ou de référence) lorsque des analyses microstructurelles sont effectuées (ce qui n'a pas été fait dans 51,4% des cas analysés).

Pour ce qui relève des défis associés à l'intégration des données IRM, nous avons dégagé certaines pratiques pertinentes ou pistes de solutions à considérer. En premier lieu, la plupart des chercheurs ont opté pour l'exportation directe des grappes d'activation IRMf (clusters) ou bien pour la création de régions d'intérêt sphériques positionnées au niveau des pics d'activation IRMf afin de guider ou filtrer la tractographie. Lorsque les analyses IRMf étaient effectuées au niveau du groupe (donc dans un espace standardisé), la procédure de normalisation inversée a été appliquée par la grande majorité afin de positionner adéquatement les régions d'intérêt dans l'espace natif IRMd des participants[11]. Dans le cas où les analyses IRMf étaient effectuées à un niveau intra-individuel (donc sans normalisation), alors les chercheurs devaient veiller à s'assurer de la bonne correspondance (coregistration) des espaces issus des différentes modalités IRM. Nous relevons que certains chercheurs ont opté pour l'application de transformations au niveau des régions d'intérêt dérivées de l'IRMf (ex. dilater ou déplacer) afin de s'assurer que celles-ci soient bien en contact avec la matière blanche pour garantir « une tractographie efficace ». Toutefois à moins de nécessité, nous ne recommandons pas cette pratique puisqu'on ne peut connaître l'impact réel de ces manipulations sur les résultats finaux de la tractographie. Qui plus est, notre analyse révèle que ce type de manipulation des données est, la plupart du temps, non nécessaire du fait que les régions d'intérêt sont souvent déjà bien en contact avec la matière blanche. Autrement, le simple fait d'utiliser des outils tels que l'ACT (anatomically constrained tractography) permet de résoudre cette problématique en permettant la tractographie dans l'intégralité des régions d'intérêt.

[11] Rappelons qu'il est recommandé d'effectuer la tractographie dans l'espace natif IRMd des participants pour éviter certaines problématiques (voir Gao et al., 2014 ainsi que Jones et Cercignani, 2010 à ce sujet).

6.2 Article #2 étude empirique

En utilisant les connaissances méthodologiques issues de l'étude de la portée, nous avons conduit cette étude empirique qui a permis de démontrer que la dénomination d'images telle qu'évaluée par la passation du Boston Naming test (BNT) chez des jeunes adules en santé (c.-à-d. sans atteinte neurodéveloppementale ou psychiatrique documentée) sollicite un vaste réseau cérébral. Ce dernier étant majoritairement périsylvien pour les aspects langagiers implique aussi des régions occipito-temporales et frontales pour les volets perceptuels et de la parole respectivement.

Au niveau de l'hémisphère gauche, l'ensemble de ces régions corticales se sont avérés structurellement interconnectés par des fibres de matière blanche formant des sous-réseaux préférentiels pour le traitement lexico-sémantique et phonologico-articulatoire. Ces sous-réseaux nous sont apparus comme correspondant aux voies ventrale et dorsale du traitement de l'information langagière.

Du côté de la voie ventrale qui, dans le cas de la dénomination d'images, permet d'associer « une image ou un son au sens et aux mots », on relève que les gyri occipital moyen, temporal supérieur, temporal inférieur, frontal inférieur ainsi que le pôle temporal sont reliées par l'entremise de l'IFOF, l'ILF, l'UF, le MdLF et l'emC.

Les données obtenues supportent l'hypothèse voulant que la voie ventrale puisse être retranchée en deux trajectoires du traitement de l'information. La première étant un chemin plus direct entre les régions occipito-temporales et le lobe préfrontal où l'information transige via le l'IFOF et l'emC. La seconde étant une trajectoire indirecte qui impliquerait, quant à elle, un relais au niveau du lobe temporal antérieur où l'information doit circuler via l'ILF et l'UF (ce point sera davantage discuté dans la section 6.3).

En ce qui concerne la voie dorsale de la dénomination d'images qui permet d'associer « les sons à la parole », elle est apparue comme étant composée des gyri temporal inférieur, temporal supérieur et précentral ainsi que de l'aire motrice supplémentaire et étant desservie par l'AF et le FAT.

Autrement, les résultats obtenus appuient aussi l'idée précédemment évoquée par Hickok et Poeppel (2004) que le gyrus temporal supérieur puisse avoir un rôle hybride au sein des voies ventrales et dorsales du langage. De façon analogue, nous avons relevé qu'en contexte de dénomination d'images le gyrus temporal inférieur postérieur pourrait aussi jouer ce rôle hybride au sein du système à deux voies de par les connexions anatomiques qu'il entretient via l'AF, l'IFOF et l'ILF (ce point sera davantage discuté dans la section 6.2).

7. Implications théoriques et cliniques

7.1 Intégration de l'IRMf pour guider la tractographie en contexte clinique?

Bien que dans le cadre de cette thèse nous n'avons pas utilisé l'intégration de l'IRMf à la tractographie auprès d'une population clinique, nous avons tout de même recueilli bon nombre d'évidences à travers notre examen de la portée qui laissent entrevoir que ceci est tout à fait faisable et même pertinent. En effet, il a été démontré que cette méthode pouvait contribuer à l'identification de biomarqueurs dans certaines pathologies (ex. maladie d'Alzheimer, schizophrénie, AVC, etc.) et qu'elle pouvait permettre de mieux guider les interventions (ex. planification de neurochirurgie pour la résection de tumeurs). Toutefois, tel que nous l'avons suggéré dans l'article, certaines précautions sont de mises. Le chercheur doit savoir que ce type d'acquisition multimodale implique pour les patients de passer une période plus prolongée dans l'appareil d'IRM. Si cela peut être convenable pour certaines populations cliniques, cela peut aussi être source de problèmes tant pour le patient que pour la qualité des données acquises (ex. inconfort, mouvement, moins bonne collaboration, etc.). Autrement, certains questionnements persistent dans la communauté scientifique à savoir si les paramètres d'acquisition IRMd et de tractographie optimisés pour la recherche auprès d'une population des jeunes adultes en santé devraient également s'appliquer pour les devis de recherche qui concernent d'autres populations (patients, enfants, personne âgées, etc.) (Cousineau, 2017; Garyfallidis et al., 2015; Schilling et al., 2019).

7.2 Réinvestissement du modèle à deux voies en contexte de dénomination

Les résultats obtenus dans l'étude #2 nous permettent de supporter l'hypothèse voulant que nos capacités de dénomination d'images soient aussi organisées en une voie ventrale qui permet d'associer « une image ou un son au sens et aux mots » et une voie dorsale qui permet d'associer « les sons à la parole » de façon analogue à ce qui a été initialement proposé par Hickok et Poeppel (2004) pour la perception de la parole (speech perception). En ce sens, les régions corticales activées en IRMf dans l'hémisphère gauche lors de la passation du BNT étaient interconnectées via des fibres de matières blanches classiquement associées à la voie ventrale ou dorsale.

Dans leur revue, Hickok et Poeppel (2004) avaient proposé que la partie postérieure du lobe temporal supérieur puisse contribuer tant à la voie ventrale que dorsale de la perception de la parole. En s'appuyant sur des données issues d'études de patients atteints d'épilepsie, d'AVC et de sujets en santé, ils proposent aussi qu'il soit possible que cette partie postérieure du lobe temporal supérieur (qui comprend le gyrus temporal supérieur [STG] et le sillon temporal supérieur [STS]) soit sous-divisée en deux modules neurocognitifs à l'origine de la voie ventrale et dorsale de la perception de la parole. Les parties ventro-antérieures étant davantage associées à la compréhension (aspects lexico-sémantiques) et les parties plus dorso-postérieures au traitement auditif et phonologique (DeWitt et Rauschecker, 2013; Hickok et Poeppel, 2004, 2016; Miglioretti et Boatman, 2003; Poeppel et Hickok, 2004; Wise et al., 2001). Il est donc intéressant de constater que la région d'intérêt retenue au niveau de la partie postérieure du STG dans l'étude #2 (coordonnées MNI -60, -36, 6) semble chevaucher la plupart de la partie postérieure du STG. Ces éléments pourraient donc expliquer pourquoi la tractographie effectuée nous a révélé la présence de connexions structurelles entre le STG et le gyrus frontal inférieur pars orbitalis (IFGpo) au sein des voies ventrale et dorsale via l'emC et l'AF respectivement.

De façon similaire, nous avons objectivé des connexions structurelles au sein de l'hémisphère gauche entre le gyrus temporal inférieur postérieur (ITG) et l'IFGpo. Celles-ci transigeaient par la voie dorsale via l'AF, mais aussi par la voie ventrale via l'IFOF. Le fait que l'ITG exhibe un patron

de connectivité structurelle via la voie dorsale est relativement surprenant lorsqu'on connaît le rôle fonctionnel de l'ITG postérieur dans la perception et le traitement sémantique visuel. Nous avons émis l'hypothèse qu'en contexte de dénomination d'images, l'ITG pourrait avoir un rôle hybride (semblable au cas du STG précédemment discuté) au sein de la voie ventrale et dorsale. Pour son implication dans la voie dorsale, son rôle pourrait être d'assister l'IFGpo dans ses requêtes phonologiques sur la base d'un percept visuel ou encore d'alimenter le STG dans son travail d'appariement des sons associés aux formes visuelles. À cet égard, nous notons que la méta-analyse de Vigneau et al., 2006 suggère que l'ITG postérieur gauche ait un rôle mixte (sémantique et phonologique) dans le langage. Néanmoins, nous suspectons que ce rôle soit partiel/indirect puisque la stimulation électrique directe de l'ITG postérieur gauche n'entraine pas d'erreurs de nature langagière durant la dénomination d'images (ex. paraphasies, anomie, néologismes, etc.) (Corina et al., 2010). Qui plus est, nous notons que la majeure des fibres qui composent l'AF concerne surtout les aires temporales supérieures et médianes ainsi que le gyrus frontal inférieur (Axer et al., 2013; Burdach, 1822; Catani et al., 2005; Dejerine, 1895; Geschwind, 1965; Makris et al., 2005; Petrides, 2013; Reil, 1809).

7.3 Reconsidérer l'implication de certaines fibres de matière blanche dans la dénomination d'images

Sur la base des résultats obtenus auprès d'une population de jeunes adultes en santé (c.-à-d. sans atteinte cognitive ou psychiatrique connue), l'étude empirique nous permet de reconsidérer et mettre à jour certaines idées/connaissances à propos de l'implication des fibres de matières blanches dans les aptitudes de dénomination d'images. En outre, ces résultats viennent également nous aider à mieux comprendre comment certaines conditions neurologiques peuvent affecter les capacités de dénomination.

En ce qui concerne l'AF gauche, l'hypothèse voulant qu'une lésion de ce faisceau cause des déficits dans la capacité de répéter et engendre de fréquentes paraphasies phonologiques a été sérieusement ébranlée au cours des années 1970 à 1990. À ce moment, une série d'études utilisant principalement des données issues de la tomographie assistée par ordinateur (CT-SCAN) ont rapporté des cas d'aphasie de conduction sans atteintes de l'AF (Damasio et Damasio, 1980;

Green et Howes, 1977; Mendez et Benson, 1985). Néanmoins, on ne peut exclure la possibilité que ces études n'aient pas réussi à objectiver des atteintes au niveau de l'AF compte tenu de la méthode d'imagerie utilisée (c.-à-d. non détectable par CT-SCAN, mais détectable par IRMd). Dans la même lignée, l'étude de Shuren et al., 1995 est parfois citée[12] comme une preuve de concept puisqu'on y rapporte le cas d'un patient qui ne présente pas de déficit de répétition à la suite d'une résection antérieure de l'AF. Cette formulation est fautive puisque Shuren et al., 1995 évoquent clairement que la capacité de répéter des pseudo-mots n'a pas été évaluée chez ce patient! Les auteurs avancent même que la parole du patient était fluente, mais qu'elle présentait des paraphasies phonologiques ("had fluent speech with occasional phonemic paraphasias"), ce qui est un symptôme cardinal pour déceler l'aphasie de conduction. Néanmoins, les résultats obtenus ainsi que la littérature présentée dans cette thèse nous permettent aujourd'hui d'affirmer avec plus d'appuie que l'AF détient un rôle clé dans la voie dorsale et au niveau du traitement phonologique.

Du côté de la voie ventrale, la combinaison de l'ILF et de l'UF pourrait agir à titre de voie ventrale indirecte pour supporter la dénomination (surtout l'accès lexical) d'items plus exigeants (ex. entités uniques comparativement aux noms communs). Cette hypothèse avancée dans la revue de la littérature de Papagno et al., 2011 met surtout l'emphase sur le rôle de l'UF dans ce processus tout en négligeant de discuter d'une potentielle implication de l'ILF. Nous proposons aujourd'hui de considérer la possibilité d'une hypothèse complémentaire à l'idée d'une unique voie indirecte qui concerne le travail conjoint de l'ILF + l'UF. Il s'agirait ici d'une seconde voie indirecte (et possiblement parallèle) qui impliquerait des échanges d'informations lexico-sémantiques via le MdLF et l'UF. Cette hypothèse retrouve d'abord un certain support à travers la description des cas d'anomie pure rapportés par Sarubbo et al., 2015 lors de la stimulation électrique directe du MdLF. À ceci s'ajoute le fait que l'anomie en contexte de dénomination de personnes célèbres chez des patients atteints de la MA corrèle avec l'atrophie de la matière grise dans la jonction temporo-pariétale gauche (c.-à-d. gyrus supramarginal et/ou angulaire) (Montembeault et al., 2017). Il est d'ailleurs intéressant de noter que cette région est réputée

[12] Par exemple au second chapitre d'un manuel classique de neuropsychologie cognitive (Handbook of cognitive neuropsychology: What deficits reveal about the human mind; 2001).

pour son implication dans l'accès lexical pour les tâches sémantiquement plus exigeantes ainsi que l'intégration sémantique intermodale (Bonner et al., 2013; Corina et al., 2010; Indefrey et Levelt, 2004; Mechelli et al., 2007; Price, 2012; Price et al., 2005). À ceci s'ajoute le fait que la jonction temporo-pariétale correspond également à une des extrémités du MdLF (Axer et al., 2013; Makris et al., 2009, 2013; Schmahmann et Pandya, 2006c; Seltzer et Pandya, 1984). Cette hypothèse complémentaire restera donc à être clarifié à l'aide de nouvelles études.

Ces éléments nous amènent encore aujourd'hui à constater que la voie ventrale est constituée d'un réseau plus complexe que la voie dorsale dans le sens où un plus grand nombre de fibres de matières blanches semblent être impliquées. Ce constat pourrait être vu comme un argument en faveur d'un réseau neurocognitif organisé de façon parallèle et distribué aussi doté d'un mode de traitement interactif. En ce sens, comme Duffau, Herbet, et al.(2013) l'ont proposé par le passé, il est possible que les voies ventrales directes et indirectes se compensent mutuellement. Cette conceptualisation de la voie ventrale pourrait expliquer pourquoi certaines atteintes de la matière blanche ou perturbation par stimulation électrique directe ne sont pas systématiquement associées à une altération des capacités de dénomination (ceci est notamment le cas de l'ILF, de l'UF et du MdLF tel qu'abordé précédemment ainsi que dans les sections 4.2.6 et 4.2.7 de cette thèse).

7.4 Débats résiduaires et conceptualisation des fibres de matière blanche chez l'humain

Malgré l'avènement des méthodes d'imagerie plus récentes dont la tractographie fait partie, l'identification précise des fibres de matière blanche chez l'humain demeure un important casse-tête pour les chercheurs. En effet, certains aspects relatifs aux fibres de matières blanches auxquelles nous avons fait référence dans cette thèse sont sujets à controverses. Il s'agit entre autres de déterminer quelles fibres de matière blanche existent réellement chez l'humain, où celles-ci débutent ou se terminent, quel nom elles devraient prendre et de déterminer leur implication fonctionnelle. L'origine de ces débats provient en grande majorité du fait que des méthodologies différentes sont utilisées (ex. comparer des données issues de la tractographie in vivo chez l'humain aux résultats d'études de traceurs radioactifs menés chez l'animal).

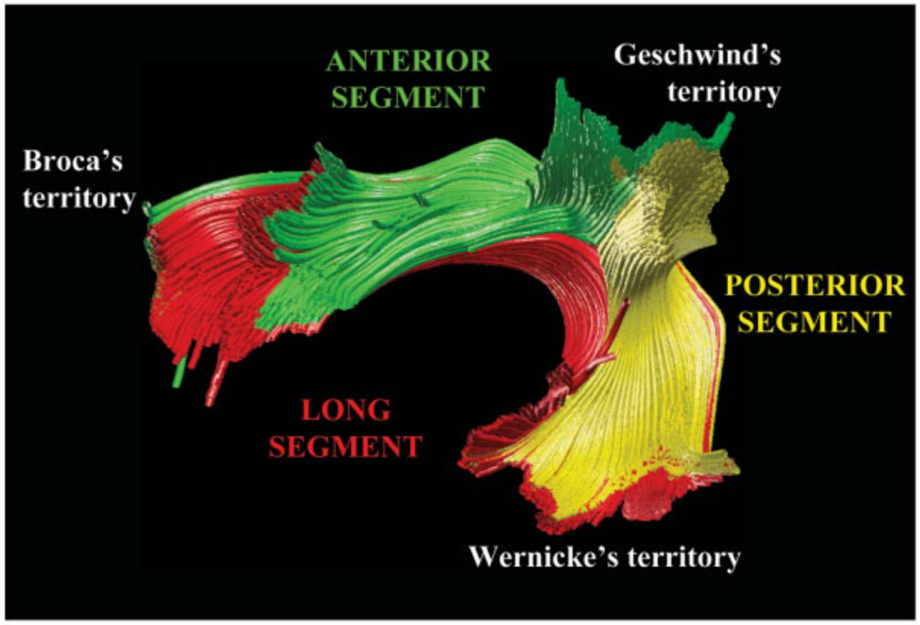
Dans un premier temps, nous nous tournerons vers la distinction entre l'AF et les SLFs en soulignant que jusqu'à relativement récemment (le début du 21e siècle), plusieurs chercheurs conceptualisaient les SLFs et l'AF comme faisant partie d'une seule et même entité (Axer et al., 2013; Makris et al., 2005). Encore aujourd'hui, il est possible de répertorier des articles qui englobent les différents tracts en faisant l'usage de l'étiquette du "AF/SLF complex". Néanmoins, des données convergentes issues d'études in vivo ainsi que post-mortem chez l'humain et les études de traceurs radioactifs chez l'animal tendent à s'accorder pour affirmer qu'il existerait trois branches distinctes du SLF (Catani et al., 2005; Dick et Tremblay, 2012; Makris et al., 2005; Petrides, 2013; Schmahmann et Pandya, 2006d). Relevons tout de même que certains auteurs ont présenté des données qui pourraient laisser croire que la troisième division ventrale (SLF-III) serait un artefact inhérent aux effets de volume partiel en IRM de diffusion (c.-à-d. lorsque le modèle DTI est utilisé) où des fibres du cingulum et de l'AF seraient mal ségréguées/catégorisées (Wang et al., 2016). Cependant, cette hypothèse n'est pas appuyée par les données issues des études animales, ni même par les études de connectivité fonctionnelle chez l'humain (Kelly et al., 2010; Margulies et Petrides, 2013; Schmahmann et Pandya, 2006d).

D'un point de vue clinique cette distinction n'est pas futile et mérite d'être sérieusement considérée puisqu'une atteinte d'une des sous branches du SLF ne devrait pas causer les mêmes impacts cognitifs qu'une atteinte de l'AF tel que cela fut présenté dans les sous-sections 4.2.1 et 4.2.2 de cette thèse (au même titre que les sous-segments du SLF contribuent à des réseaux cérébraux distincts). Ainsi, l'utilisation du terme ambigu "AF/SLF complex" serait à proscrire.

Une autre partie de la confusion relative à l'AF et au SLF semble attribuable à l'ambigüité conceptuelle de l'AF (encore ici, potentiellement lié au choix de la méthode d'investigation choisie). En ce sens, il est possible de retrouver des définitions de l'AF alternatives à celle que nous avons retenue dans cette thèse. Par exemple, sur la base de la tractographie (par imagerie de diffusion de tenseur / DTI) , Catani et al., 2005 ont proposé une conception tripartite de L'AF (voir figure 1 ci-bas). On y retrouve d'abord un segment long qui correspond davantage à la définition de l'AF que nous avons présentée dans la sous-section 4.2.1, mais aussi un segment antérieur qui correspondrait similairement au SLF-III présenté dans les sous-sections 4.2.2 ainsi qu'un segment postérieur organisé de façon perpendiculaire/ascendante qui relierait le lobe

temporal au lobe pariétal inférieur. Pour une revue détaillée sur le sujet, nous invitons le lecteur à consulter l'article de Dick et Tremblay, 2012.

Figure 1. – Représentation schématique de l'AF (selon Catani et al. 2005)



Parallèlement à ceci, le choix d'utiliser le terme faisceau temporo-frontal de la capsule extrême (emC), peut susciter la controverse pour diverses raisons. Dans un premier temps, relevons que le terme capsule en neuroanatomie est supposé faire référence à une localisation anatomique par où les fibres de matières blanches convergent temporairement pour trouver passage vers une autre destination (ex. corona radiata → capsule interne → faisceau cortico-spinal) (Bajada et al., 2015; Shekari et al., 2021). Dans un second lieu, divers auteurs suggèrent que l'emC tel qu'initialement décrit par certains chercheurs (Petrides et Pandya, 1988; Schmahmann et Pandya, 2006a) via les études comparatives animales n'existerait pas chez l'humain. l'idée étant que l'IFOF aurait remplacé l'emC dans l'évolution de notre espèce (Duffau, Herbet, et al., 2013; Thiebaut de Schotten et al., 2012). Toutefois, ce raisonnement ne semble pas tenir la route puisque 1) des études de tractographie chez l'humain appuient l'existence de l'emC (Anwander et al., 2007; Frey et al., 2008; Makris and Pandya, 2009; Saur et al., 2008), 2) une étude combinant la dissection

post-mortem et l'imagerie par lumière polarisée reconnait aussi l'emC humain (Axer et al., 2013) et 3) les études en IRMf chez l'humain qui démontrent des patrons de connectivité fonctionnelle entre les points terminaux de l'emC (les aires temporales médianes ou supérieures, lobule pariétal inférieur et cortex préfrontal ventrolatéral) (Margulies et Petrides, 2013). Qui plus est, l'IFOF dans sa description canonique ne concerne pas les gyri temporaux médians ou supérieurs (Catani et Thiebaut de Schotten, 2008; Curran, 1909; Fernández-Miranda et al., 2008; Martino et al., 2010; Petrides, 2013). Ainsi, certains ont proposé de diviser l'IFOF en deux sous composantes. Selon cette perspective, il existerait un segment superficiel (ou dorsal) de l'IFOF qui relierait le gyrus temporal supérieur et le lobule pariétal supérieur au cortex préfrontal ventrolatéral et un segment profond ou ventral (« deep layer ») qui correspond à la description canonique de l'IFOF (Duffau, Herbet, et al., 2013; Sarubbo et al., 2013). Bien que cette proposition soit pertinente, elle comprend aussi ses limitations du fait que les extrémités proposées ne correspondent pas à l'emC et, encore ici, son nom (segment superficiel de l'IFOF) suggère des connexions occipito-frontales et non temporo-frontales.

Plus récemment, une nomenclature alternative aux nomenclatures classiques a été proposée pour rendre compte des divergences ci-haut évoquées (Mandonnet et al., 2018). Il est intéressant de constater que dans cette proposition, les auteurs semblent avoir préconisé les définitions de l'AF et du SLF que nous avons retenus dans cette thèse. Qui plus est, les auteurs proposent l'existence d'un système de fibres associatives transversales postérieures qui s'apparente beaucoup à la description du segment postérieur de l'AF de Catani et al. 2005.

8. Considérations méthodologiques

8.1. Complémentarité des études

D'un point de vue méthodologique, les deux études présentées dans le cadre de cette thèse se veulent complémentaires. Dans un premier temps, l'examen de la portée effectué dans l'étude#1 nous a permis de nous informer à propos des pratiques courantes en ce qui concerne l'intégration de l'IRMf pour guider la tractographie. Au-delà de cet aspect, nous avons surtout pu procéder à un examen critique d'un vaste éventail d'études (80 études) et retenir les meilleures pratiques/recommandations. Ainsi, notre projet de recherche empirique peut agir à titre de

preuve de concept en ce qui concerne la faisabilité et l'applicabilité de ces dernières. Qui plus est, grâce à la publication de l'étude de la portée, ces informations sont maintenant disponibles à la communauté scientifique qui pourra en bénéficier afin d'améliorer la qualité des futures études qui intègreront l'IRMf pour guider la tractographie.

8.2. IRM multimodale et triangulation des résultats

Pour le volet IRMf, le fait d'avoir opté pour un niveau de base simple (bas niveau / croix de fixation) combiné à un mode de réponse oral (« overt vocalization ») nous a permis de répertorier des activations cérébrales qui vont au-delà des aspects strictement langagiers. Ceci nous a donc offert un tableau plus complet et plus riche qui implique aussi les éléments perceptuels et de la parole associés à la dénomination d'images.

Par la suite, notre approche multimodale de l'intégration de l'IRMf (contraste basé sur la tâche) pour guider la tractographie nous a permis de faire le pont entre le réseau fonctionnel de la dénomination d'images et les fibres de matières blanches qui y garantissent les échanges d'information.

L'étude empirique a été faite à l'aide d'un échantillon unique, ce qui correspond aussi à une considération méthodologique abordée dans le cadre de notre étude de la portée. Le fait d'avoir ciblé une population de jeunes adultes en santé (c.-à-d. sans problème cognitif ou psychiatrique connu) permet de contourner certaines limites inhérentes à l'étude de patients (ex. hétérogénéité des caractéristiques sociodémographiques, condition pré morbide inconnue, hétérogénéité de l'étendue des atteintes cognitives ou cérébrales, etc.). De plus, notre intention était de documenter le réseau fonctionnel et les connexions structurelles typiques (« normales ») impliqués dans la dénomination d'images telle qu'évaluée par le BNT.

Plusieurs mesures ont été mises en place dans le protocole d'analyses des données de l'étude empirique afin de valider et vérifier la plausibilité des tracks fonctionnellement définies obtenues (c.-à-d. les tracks provenant de la tractographie effectuée entre les régions d'intérêt issues de l'IRMf). Tout d'abord, nous avons utilisé la méthode ACT (Smith et al., 2012) afin de réduire les possibilités d'obtenir des erreurs de type 1 (faux positifs) lors de la tractographie. Nous avons aussi vérifié le taux de reproductibilités des tracks fonctionnellement définies à travers les

participants (voir le tableau 3 de l'article 2). Cette dernière procédure nous a notamment permis de mettre en doute l'existence d'une connexion structurelle directe entre le MOG et l'IFGpo puisque ce scénario était uniquement reproductible sur 31% de l'échantillon. L'appartenance des tracks[13] fonctionnellement définies à des tracts de matière blanche connus a également été examinée via des analyses quantitatives (voir tableau 5 et tableau supplémentaire 4) et qualitatives (voir figure 5) de leur chevauchement. Finalement, une emphase particulière a été mise sur la triangulation des résultats obtenus dans l'étude empirique en présentant de multiples données convergentes issues de méthodologies complémentaires et de recherches indépendantes (ex. stimulation électrique directe, études animales comparatives, dissection post-mortem, imagerie cérébrale auprès de patients et d'individus en santé, etc.). Ce dernier aspect méthodologique correspondait aussi à une recommandation relevée par notre étude de la portée afin d'améliorer la validité et la spécificité des résultats.

9. Limites des études

Une des limites de notre étude de la portée concerne le fait que nous avons uniquement analysé les études ayant effectué des analyses de contrastes basées sur la tâche en IRMf pour guider la tractographie. Ceci implique donc que tous les articles ayant guidé la tractographie à partir de donnée issue d'analyses de connectivité fonctionnelle via des protocoles de type état de repos (« resting-state ») ont été ignorés. Une analyse à postériori de nos données brutes issues de notre recherche documentaire nous permet d'affirmer qu'il s'agirait là de 20 études supplémentaires.

Du côté de l'étude empirique, il pourrait être argumenté que le fait d'avoir eu recours à des acquisitions IRMd de type « single shell » pourrait avoir diminué la qualité de nos données/résultats. Toutefois, il faut savoir qu'au moment de l'acquisition de données IRMd (2015 et 2016), les séquences d'IMRd de type « multishell » n'étaient pas encore disponibles à notre site d'acquisition.

[13] Rappel: Afin de respecter la nomenclature établie au sein de la littérature scientifique, veuillez noter que le terme « track » sera utilisé dans cet ouvrage pour faire référence au produit/résultat de la tractographie alors que le terme « tract » sera réservé pour désigner l'entité anatomique (c.-à-d. les faisceaux de matière blanche).

Autrement, le fait d'avoir choisi d'uniquement effectuer la tractographie au sein de l'hémisphère gauche a très certainement réduit l'ampleur du travail computationnel nécessaire à la tractographie en diminuant le nombre de connexions structurelles à investiguer entre les régions cérébrales significativement activées. Toutefois, cela nous a privé de l'opportunité d'étudier la contribution de l'hémisphère droit dans la dénomination d'images ainsi que l'implication des connexions inter-hémisphériques (ex. le très volumineux corps calleux). Également, nous n'avons pas étudié les connexions cortico-thalamiques, cortico-striées et cortico-cérébelleuses pouvant être pertinentes dans la dénomination d'images.

10. Contributions originales de la thèse

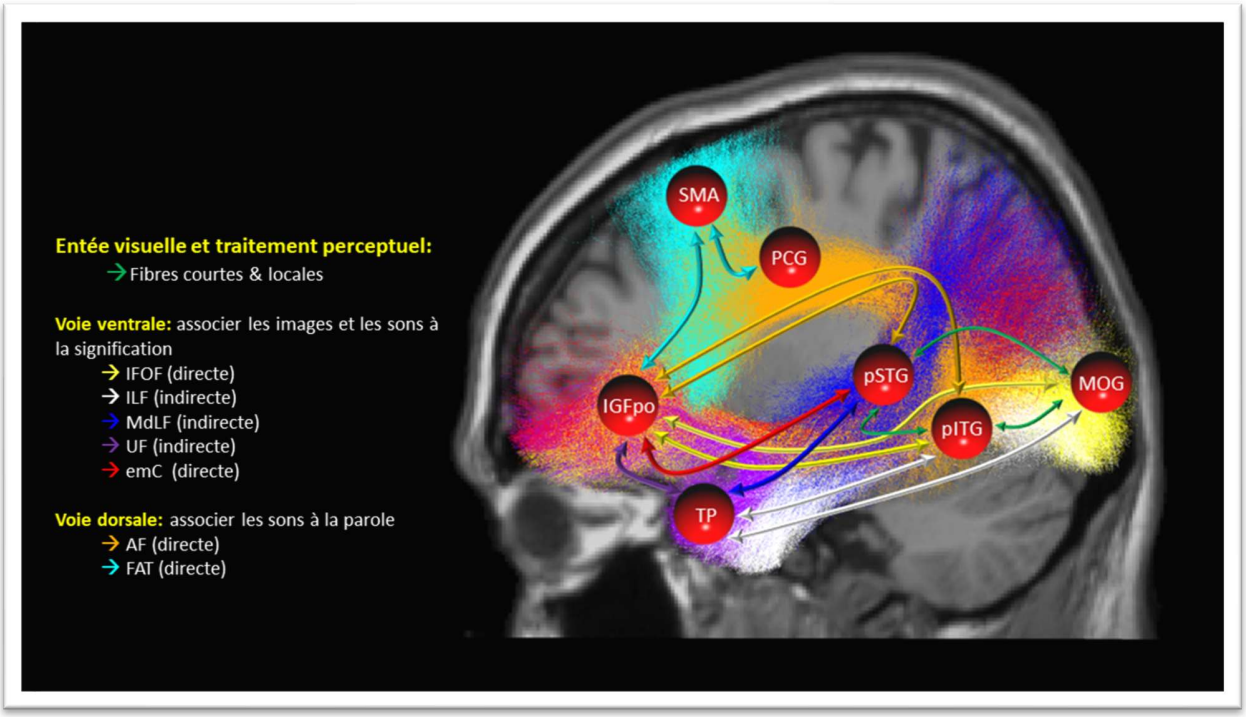
Cette thèse propose plusieurs contributions originales dans les domaines de la neuroimagerie et de la neurobiologie du langage dont bon nombre ont déjà été couvertes dans le cadre de ce chapitre.

Pour commencer, l'examen de la portée est la première étude qui propose une approche systématique (étude de la portée) afin d'analyser, synthétiser la littérature de 80 études ayant intégré l'IRMf afin de guider la tractographie. De plus, ce document se veut un outil pratique qui propose des recommandations et oriente vers les meilleures pratiques dans l'application de cette méthode d'intégrative des données IRM multimodale. Les connaissances dégagées par cette étude initiale nous ont ensuite permis d'améliorer la qualité de l'étude empirique qui impliquait l'intégration de l'IRMf pour guider la tractographie.

Dans un deuxième temps, le second article proposé est également pertinent puisqu'il nous permet aujourd'hui de proposer un modèle neurocognitif de la dénomination d'images (voir figure 2 ci-bas) tel qu'évalué par le Boston Naming Test (BNT), l'un des outils d'évaluation les plus couramment utilisés (Bortnik et al., 2013; Strauss et al., 2006). Ce modèle se veut plus complet que la plupart des modèles existant puisqu'il tient compte simultanément des régions corticales de l'hémisphère gauche ainsi que l'implication des fibres de matière blanches sous-jacente en plus d'associer ces structures aux étapes du traitement de l'information les concernant (ex. traitement perceptuel, sémantique, lexical, phonologique et articulatoire). Cette proposition permet également d'adapter plus formellement le modèle à deux voies de la perception de la

parole (Hickok et Poeppel, 2004) au contexte de la dénomination d'image (production langagière). Le tout se base non seulement sur les résultats empiriques obtenus auprès de jeunes adultes en santé, mais aussi sur l'intégration riche des données issues des populations cliniques répertoriées dans la littérature (triangulation des résultats issues des études suivantes : Agosta et al., 2010; Baldo et al., 2013; Brambati et al., 2006; Corina et al., 2010; De Witt Hamer et al., 2011; Dick et al., 2019; Duffau et al., 2003, 2009; Duffau, Moritz-Gasser, et al., 2013; Galantucci et al., 2011; Kinoshita et al., 2015; Mandonnet et al., 2007; Ojemann et al., 1989; Papagno, 2011; Papagno et al., 2011; Penfield, 1959; Penfield et Rasmussen, 1950; Price et al., 2005; Sarubbo et al., 2015; Saur et al., 2008b; Shinoura et al., 2010; Turken et Dronkers, 2011; Vigneau et al., 2006; Xing et al., 2018). En somme, cette étude a le potentiel d'être utile tant pour la communauté scientifique pour mieux comprendre notre capacité à nommer des images/objets, mais aussi pour les cliniciens afin de mieux comprendre l'origine des difficultés de dénomination chez les patients.

Figure 2. – Modèle neurocognitif de la dénomination d'images



11. Avenues de recherches futures

Les études présentées dans le cadre de cette thèse nous ont offert l'opportunité d'identifier des flous ou des lacunes au sein des connaissances.

En ce qui concerne les aspects méthodologiques associés à l'intégration de l'IRMf pour guider la tractographie, il serait pertinent d'étudier l'impact de l'application de mesures de transformation au niveau des régions d'intérêt dérivées de l'IRMf (ex. dilater ou déplacer) visant à garantir « un meilleur contact » avec la matière blanche. On pourrait également évaluer si le fait d'avoir recours à des échantillons (ou bases de données) indépendants (ex. données IRMf recueillies auprès d'un groupe A et données IRMd recueillies auprès d'un groupe B) est problématique ou non. Ceci pourrait entre autres permettre d'utiliser les bases de données IRMd (ex. Human Connectome Project) et de guider la tractographie à partir des données/résultats d'activation IRMf issues de différentes études ou, encore mieux, de méta-analyses.

Autrement, il serait pertinent d'apporter davantage de clarifications relativement à l'implication de l'ILF, de l'UF et du MdLF dans la dénomination. Pour ce faire, on pourrait avoir recours au profilage tractométrique pour corréler les propriétés microstructurelles de ces fibres de matière blanche au niveau de performance de participants dans des tâches comportementales telles que la dénomination d'images et la dénomination d'entité unique (ex. personnes célèbres). Idéalement, il faudrait un échantillon qui comporte des patients (ex. MA, sv-PPA ou AVC) et des participants contrôle.

12. Conclusions

En somme, cette thèse nous a permis de documenter de façon très exhaustive les pratiques liées à l'intégration de l'IRMf pour guider la tractographie, d'en dégager les principales lacunes et d'offrir des recommandations ou pistes de solution à considérer afin d'améliorer la qualité méthodologique des études ultérieures. Dans un deuxième temps, le travail associé à ce doctorat a permis de démontrer l'applicabilité de ces éléments méthodologique à travers une étude empirique impliquant l'intégration de l'IRMf pour guider la tractographie. Au-delà des aspects méthodologiques, ce travail de recherche a permis d'élaborer un modèle neurocognitif de la

dénomination d'images qui offre une vision intégrative de la cognition, des réseaux fonctionnels (IRMf) et des connexions structurelles sous-jacentes (les fibres de matière blanche). Dans l'ensemble, ces informations seront utiles pour la communauté scientifique, mais aussi pour les cliniciens qui œuvrent auprès de patients qui éprouvent des difficultés langagières.

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Annexes