REVIEW ARTICLE

White matter tracts and executive functions: a review of causal and correlation evidence

Monica Ribeiro,[1,2] Yordanka Nikolova Yordanova,[3] Vincent Noblet,[4] Guillaume Herbet[5,6,7] and Damien Ricard[2,8,9]

Abstract

Executive functions are high-level cognitive processes involving abilities such as working memory/updating, set-shifting and inhibition. These complex cognitive functions are enabled by interactions among widely distributed cognitive networks, supported by white matter tracts. Executive impairment is frequent in neurological conditions affecting white matter; however, whether specific tracts are crucial for normal executive functions is unclear. We review causal and correlation evidence from studies that used direct electrical stimulation during awake surgery for gliomas, voxel-based and tract-based lesion-symptom mapping, and diffusion tensor imaging to explore associations between the integrity of white matter tracts and executive functions in healthy and impaired adults. The corpus callosum was consistently associated with all executive processes, notably its anterior segments. Both causal and correlation evidence showed prominent support of the superior longitudinal fasciculus to executive functions, notably to working memory. More specifically, strong evidence suggested that the second branch of the superior longitudinal fasciculus is crucial for all executive functions, especially for flexibility. Global results showed left lateralization for verbal tasks and right lateralization for executive tasks with visual demands. The frontal aslant tract potentially supports executive functions; however, additional evidence is needed to clarify whether its involvement in executive tasks goes beyond the control of language. Converging evidence indicates that a right-lateralized network of tracts connecting cortical and subcortical grey matter regions supports the performance of tasks assessing response inhibition, some suggesting a role for the right anterior thalamic radiation. Finally, correlation evidence suggests a role for the cingulum bundle in executive functions, especially in inhibition tasks. We discuss these findings in light of current knowledge about the functional role of these tracts, descriptions of the brain networks supporting executive functions

and clinical implications for individuals with brain tumors.

Author affiliations :

1 Service de neuro-oncologie, Hôpital de la Pitié-Salpêtrière-Charles Foix, Sorbonne Université, 75013 Paris, France

2 Université de Paris Saclay, ENS Paris Saclay, Service de Santé des Armées, CNRS, Université de Paris Cité, INSERM, Centre Borelli UMR 9010 75006 Paris, France

3 Service de neurochirurgie, Hôpital d'Instruction des Armées Percy, Service de Santé des Armées, 92140 Clamart, France

4 ICube, Université de Strasbourg, CNRS, UMR 7357, Strasbourg, France

5 Praxiling, UMR5267, CNRS, Université Paul Valéry Montpellier 3, Montpellier, France

6 Département de Neurochirurgie, Hôpital Gui de Chauliac, Centre Hospitalier Universitaire de Montpellier, 34295 Montpellier, France

7 Institut Universitaire de France

8 Département de neurologie, Hôpital d'Instruction des Armées Percy, Service de Santé des Armées, 92140, Clamart, France

9 Ecole du Val-de-Grâce, 75005 Paris, France

Running title: White matter tracts and executive functions

Keywords: superior longitudinal fasciculus; cognitive control; diffusion tensor imaging; awake surgery; voxel-based lesion-symptom mapping; tract-based lesion-symptom mapping

Abbreviations: AF = arcuate fasciculus; CC = corpus callosum; CR = corona radiata; DES = direct electrical stimulation; D-FPN = dorsal fronto-parietal network; DKI = diffusion kurtosis imaging; DTI = diffusion tensor imaging; EC = external capsule; FA = fractional anisotropy; FAT = frontal aslant tract; FPN = fronto-parietal network; IC = internal capsule; IFG = inferior frontal gyrus; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; L-FPN = lateral fronto-parietal network; M-CIN = midcingulo-insular network; MD = mean diffusivity; PFC = prefrontal cortex; SMA = supplementary motor area; SLF = superior longitudinal fasciculus; pre-SMA = pre-supplementary motor areas; ROI = Region of Interest; TMT-B = Trail Making Test B; TR = thalamic radiation

Introduction

Complex and flexible cognitive processes are underpinned by widely distributed neural systems in the human brain,[1–3] connected by white matter tracts that support structural connectivity, thus enabling information transfer among brain areas and network integration. The central role of white matter in human behavior and learning has been demonstrated in studies showing clear associations between its abnormalities and a wide range of cognitive deficits, from basic information processing speed to high-level processes such as executive functions.[4–6]

Interest in white matter function has been increasing as conceptions of brain functioning have evolved from localizationist to network models. In localizationist models, brain functions are associated with and attributed to the activity of specialized brain areas,[7]whereas current conceptions describe brain functions emerging from flexible, dynamic and parallel interactions among distant and hierarchically organized networks of cortical and subcortical zones.[2] Descriptions of brain architecture and networks[8–10] have provided an account of brain network organization, properties and function not only at the cortical level but also in terms of subcortical connectivity.[11,12] More than just connectors, myelinated fibers reinforce the speed of conduction, and the connectivity of the white matter tracts allows the rapid synchronization of information among cortical regions.[2,11,13] In other words, white matter tracts support synaptic function underlying information processing and connect remote grey matter zones into communicating neural assembles. In this vein, current neuroanatomical models explaining brain dysfunction combine the roles of cortical brain zones and axonal connections in a “hodotopical” approach.[14]According to this theoretical framework, brain dysfunction may result from “topological” mechanisms (i.e., cortical lesions) or “hodological” mechanisms (i.e., lesions in axonal pathways underlying connections among brain zones).

In light of these descriptions, disconnection mechanisms have been hypothesized to explain cognitive dysfunction associated with brain pathologies affecting white matter such as traumatic brain injury,[15–17]multiple sclerosis[18,19]andc erebrovascular disease, for example.[20]Also, disconnection mechanisms and dysfunction of neural networks are thought be involved in the marked executive and functional impairment associated with neuropsychiatric conditions such as major depression, bipolar disorder and schizophrenia.[21,22] White matter has been much studied in normal aging processes[23]: white matter microstructure damage and subsequent disconnection mechanisms are a central hypothesis explaining the decline or change in cognitive functioning.[24–27]Changes in brain architecture related to glioma growth and subsequent post-lesional neuroplasticity clearly revealed the key role of white matter, particularly regarding the dynamics underlying the flexible functioning and recovery potential of the central nervous system.[28,29] Diffuse low-grade gliomas develop slowly by infiltrating white matter. This induces neuro-synaptic reorganization and recruitment of adjacent or even contralateral zones for functional compensation of damaged areas, leading to significant changes in neural network architecture.[30] These changes give opportunities for optimal tumor resection, because resection boundaries can be defined according to individual perioperative responses triggered during direct electrical stimulation (DES),[31] as long as subcortical connectivity is identified and preserved.[29,32]

Impairment of executive functions (Box 1) is indeed a common and perhaps a core deficit in brain conditions with predominant white matter damage.[33–35] Such deficits may severely compromise independence and quality of life because of their impact on professional, social, and emotional functioning.[36]

Neural networks supporting executive functions

Various techniques such as functional MRI (fMRI) including resting state and activation fMRI, electrophysiology and lesion studies have provided evidence leading to descriptions of large-scale brain networks involving frontal, parietal, and insular regions.[72–75] These regions form distinct neural systems with specific roles in directing the cognitive process toward the achievement of goal-directed behaviors.[76]

According to a review article that introduced a new taxonomy for the large-scale functional networks in the human brain,[77]three functional networks would be prominently involved in executive functions: the dorsal fronto-parietal (D-FPN), lateral fronto-parietal (L-FPN) and midcingulo-insular (M-CIN) networks. The D-FPN or dorsal attention network, supports visuospatial attention by preparing and exerting top-down selection for stimuli and responses.[75] It includes the superior parietal lobule extending into the intraparietal sulcus, middle temporal complex and the putative frontal eye fields as core regions and would involve the ventral premotor cortex.[74,75]The L-FPN supports goal-directed control of information flow.[78,79]It comprises the lateral prefrontal cortex (PFC), along the middle inferior parietal lobule (including rostral and dorsolateral PFC) and the anterior inferior parietal lobule into the intraparietal sulcus as core regions, involving as well the midcingulate gyrus.[80]It has been described as a domain general system for a wide variety of demanding cognitive tasks.[81,82] Meta-analyses showed convergence of activations for the three executive domains in this system,[83,84] that has been associated with the common EF factor[44,45] in studies exploring the unity and diversity of the neural substrates of executive functions.[85,86]Also, the M-CIN, a right lateralized system, is thought to direct attention to spatial locations of salient stimuli and maintain task sets in demanding cognitive tasks. Core regions are the bilateral anterior insulae and anterior midcingulate cortex. Other involved regions are the inferior parietal cortex,[80] right temporal parietal junction and lateral PFC,[75,79]as well as subcortical structures including the basal ventromedial nucleus of the thalamus.[72,77,87]

Regarding executive constructs, meta-analyses using activation likelihood estimation revealed several overlapping and also specific patterns of activations within these large-scale networks during performance of executive tasks. Working memory/updating tasks consistently activate a bilateral network of frontal and parietal regions regardless of the type of stimuli, including bilateral inferior frontal gyri (IFG), bilateral pre-supplementary motor areas (pre-SMA), bilateral intraparietal sulci and bilateral anterior insulae, described as the “core” working memory network.[88]Task-switching paradigms also activate widely distributed networks depending on task features but the medial PFC, lateral PFC, especially the inferior frontal junction,[58,60]ventrolateral PFC, posterior parietal cortices, insula and anterior cingulate cortices are described as domain-general regions for flexibility.[58,60,89–91]Finally, meta-analysis of domain-general regions for tasks assessing inhibition identified a right-lateralized network of cortical regions including the IFG, insula, median cingulate and paracingulate gyri and superior parietal gyrus[68]that are consistently active across studies using different tasks. Other previously described core nodes such as the pre-SMA and subcortical structures[27,63,67,92–94]were engaged in resolving interference (i.e. the Stroop task) and in response inhibition requiring action withholding (i.e., Go-No Go tasks).[68]

In light of these findings, there is growing interest in investigating white matter structures underlying interactions among these networks in the healthy and diseased brain. Recent years has seen an increase in knowledge of the functional role of white matter tracts in motor, language, visuospatial processing and other cognitive processes, according to results from lesion studies and the neuro-oncology field.[28,95–97]The crucial role of the connectivity underlying the FPN for executive functions has been demonstrated in diffusion MRI and voxel-based lesion-symptom mapping studies.[26,98,99]However, studies exploring relations between white matter integrity and cognition usually report different groups of white matter bundles associated with performance on one or more cognitive tasks,[100] providing heterogeneous results. We still do not know whether specific tracts can prominently support executive functions (i.e., tracts consistently associated with executive functions across tasks, populations, and according to different levels of evidence).[100]

The objective of this review was to identify the white matter tracts consistently associated with performance on tasks assessing executive functions, according to results from studies using DES, lesion mapping and diffusion MRI techniques.(Box 2) We focused on the three constructs defined in the unity/diversity of executive functions model, commonly assessed in in clinical practice[36,44]and research,[83,84]namely working memory/updating, set-shifting and inhibition of prepotent responses.[40,44]

Methods

We searched PubMed for studies published from 2009 to 2023 that explored associations between executive functions and integrity of white matter tracts in healthy and cognitively impaired human adults. The searches were conducted using general and specific terms related to executive processes and techniques used to explore white matter. Executive tasks commonly used in clinical practice and research were included in the search terms, to retrieve studies that explored general cognition or used composite scores. We also included attentional processes to the search terms, to retrieve studies that explored attention using executive tests. The following terms were used: “anti-saccade”, “attentional control”, “attentional set shifting”, “cognitive control”, “executive functions”, “flexibility”, “inhibition”, “inhibitory control”, “interference control”, “selective attention”, “set shifting”, “sustained attention”, “task switching”, “updating”, “working memory”, “digit spans”, “n-back”, “Go No Go”, “Stop signal task”, “Stroop task”, “Trail Making Test”, “Tower of London”, “Wisconsin Card Sorting Test”, combined with "awake surgery", "diffusion tensor imaging", "tract-based lesion-symptom mapping", "voxel-based lesion-symptom mapping", "white matter". We selected studies and reviewed references of included studies that could be relevant.(Fig.1) The procedures used in each study to avoid bias and validate their methods were rated according to PRISMA guidelines,[121]using a checklist adapted from previous work.[122] (Supplementary material) Briefly, we used the following basic criteria to rate the studies: sufficient description of population sources and report of confounders, sufficient detail of the protocol for reproducibility, type of task and task parameters used for studying associations with white matter parameters. Studies included in the main results provided sufficient anatomical description/delineation of white matter tracts.

Results

In the following sections, we summarize findings according to different levels of evidence, from causal to correlational: for each executive process, we present convergent findings for different white matter tracts, from lesion analyses and DES during awake surgery, followed by results from diffusion MRI studies of healthy and clinical populations. For neuroimaging evidence, we focused on studies using whole brain voxel wise analyses; studies using anatomical regions of interest (ROI) were selected according to methods and rationale.

Working memory

Causal evidence

Results from lesion studies and awake surgery have provided strong evidence for the role of the superior longitudinal fasciculus (SLF), connecting the superior parietal to superior frontal lobes longitudinally along the dorsal premotor and dorsolateral prefrontal regions[123]in working memory. Kinoshita *et al.*[124] used voxel-based lesion-symptom mapping, DES and a visuospatial 2-back task paradigm to assess visuospatial working memory retrospectively and at least 6 months postoperatively in patients who underwent craniotomy under general anesthesia for right prefrontal glioma. As compared with healthy controls and two patients who had undergone awake surgery, the performance of patients operated under general anesthesia at follow-up assessment was significantly lower, and correlated with lesions in the region overlapping the SLF-I (dorsal part) and II (middle part).[125] These results agree with several findings pointing to a major role for the SLF in supporting interactions among a right-lateralized system underlying visuospatial attention[75,126–128]within the D-FPN.[77]According to descriptions of functional differentiation of its segments,[128]the SLF-I would be involved in the voluntary orienting of spatial attention (i.e., the top-down, dorsal attention network)[75]and the SLF-II would modulate communication between the dorsal and ventral attention network, a system that directs attention to spatial location of salient stimuli.[75,80]

In a study of 29 patients undergoing awake surgery for removal of neoplastic lesions in the left hemisphere, those performing the digit spans task while receiving DES in the left SLF-III (ventral part) made order errors rather than item errors, but no language deficits were elicited.[129]The authors propose that the SLF-III would underlie the transferal of order information from the phonological store of the inferior parietal lobule to Broca's area, in other words, supporting the working memory phonological loop.[55]

Verbal working memory deficits have been associated with lesions in a crossroad of white matter pathways comprising the SLF (primarily branch 1) but also the frontal aslant tract (FAT) and fronto-striatal tracts, in the left hemisphere.[130]Connecting the inferior frontal gyrus with the anterior cingulate cortex and medial regions of the superior frontal gyrus (i.e., pre-SMA and SMA), the FAT has only recently been described[131]although previously identified in models of inhibitory control.[132] Evidence from DES and clinical studies points to a prominent role of the left FAT in language and in speech initiation.[133–135]In the right hemisphere, its support of executive functions has been hypothesized because it underlies a right-lateralized system involved in cognitive control including the inferior frontal gyrus, the pre-SMA and subcortical structures[132,134,136] (i.e., regions integrating the L-FPN).[77]One case report of awake surgery described the patient's inability to cite digits backwards during DES of the right FAT, whereas digit spans forward were normally performed.[137]Associations with working memory would be possible given the central role of the pre-SMA and SMA in verbal and non-verbal working memory tasks.[88,138,139]

Concerning the fronto-striatal tract (also called the subcallosal fasciculus), connecting the SMA to the caudate nucleus,[102]causal evidence showed its support of motor inhibition[135]and, in the left hemisphere, speech initiation.[102,135,140]Considering these findings and the role of the caudate in subcortical-cortical modulation of goal-directed cognition and action,[136,141,142] the fronto-striatal tracts could have at least an indirect role in the flexible manipulation of verbal information in working memory.

Correlation evidence

In studies involving whole brain analyses of healthy individuals across ages[143–149] and in clinical populations,[150,151]the integrity of the different segments of the corpus callosum (CC) has been consistently associated with working memory assessed with different tasks. This was confirmed in a study including a large group and controlling for multiple factors modulating performance, including processing speed.[152]The CC genu, connecting symmetrical dorsolateral prefrontal regions,[123] has been most consistently associated with working memory performance, in studies exploring age-related decline in working memory performance.[143–145,147,148]

The integrity of the SLF has been strongly correlated with working memory capacity, including in large samples of healthy individuals.[147,153] In analyses exploring brain networks underlying working memory, higher FA in bilateral SLF modulated both performance at a high load of working memory capacity and brain blood oxygenation responses within the FPN.[154] It has also supported better reconfiguration of networks from resting state to performance conditions, contributing to better n-back performance.[155]Other studies exploring the effects of working memory training on white matter plasticity using visual and verbal tasks have shown gains in performance in healthy young and older adults associated with decreased MD (i.e., increased myelination) in the right SLF,[156,157]right SLF-I and left SLF-II.[156]Similar associations have been reported in clinical populations,[150,151,158,159]some based on DKI metrics.[158]In other analyses, activations of cortical networks involved in working memory supported such findings.[151] Moreover, DTI metrics in the arcuate fasciculus (AF) have been correlated with verbal working memory performance, in a large sample of healthy aging individuals[147] and in individuals with traumatic brain injury.[150] The AF is a lateral bundle lying close to the SLF-III, connecting the perisylvian cortex of the frontal, parietal, and temporal lobes.[160]

The number of DTI studies presenting results for the cingulum bundle, connecting the cingulate cortex to numerous brain regions through short and long fibers,[161]is limited. However, working memory performance has been correlated with the integrity of this tract in large samples of healthy aging individuals.[145,162] One study showed the involvement of the bilateral anterior and posterior parts of the cingulum.[145] In smaller populations, analyses of training-induced plastic changes within fronto-parietal regions showed a significant effect on both working memory capacity and integrity of parahippocampal segments of the left cingulum, suggesting its support of working memory.[156]

Despite a hypothesized putative role of the FAT in executive functions,[134]studies using whole brain analyses did not report correlations. In ROI analyses restricted to language-associated pathways, FA in the bilateral FAT has been correlated with performance in working memory in healthy aging individuals.[153] Also, in a study exploring the functional differentiation of the FAT in a larger sample, fiber density of its anterior right segments has been associated with n-back performance,[163,164] with left segments correlated with language.[164]

Less consistently, other associative and projection tracts have been correlated with performance on n-back tasks in clinical populations, such as the fornix,[150] connecting the medial temporal lobe to the mammillary bodies and hypothalamus and belonging to the limbic system[160]; the inferior longitudinal fasciculus (ILF),[151]a ventral associative bundle connecting the occipital and temporal lobes; and the inferior fronto-occipital fasciculus (IFOF),[151]connecting the ventral occipital lobe and the orbitofrontal cortex.[160]

Results from studies of large groups of healthy individuals suggest the involvement of fibers supporting cortico-subcortical networks in working memory performance. Some showed significant correlations with DTI metrics in the internal capsule (IC),[143,152] MD[147]and DKI[149] indexes in the left superior and posterior corona radiata (CR). The IC and CR contain ascending fibers from the thalamus to the cerebral cortex and descending fibers from the fronto-parietal cortex to the subcortical nuclei.[160]Other studies showed significant correlations with MD and FA in the external capsule (EC),[145,165]transporting fibers from prefrontal, temporal, SMA and pre-occipital regions to the caudate and putamen. Along with low integrity of the EC, low performers of n-back tasks had low connectivity within the FPN and between the FPN and the striatum.[165]Moreover, in whole brain analyses using sensitive models to detect structural changes in white matter microstructure, the integrity of the posterior thalamic radiation (TR), carrying fibers between the thalamus and the PFC, was significantly correlated with working memory performance in individuals with psychiatric disorders.[166]

Summary

Taken together, evidence supports the prominent role of the CC and the SLF in working memory.

According to causal evidence, the left SLF-I was associated with verbal working memory[130]; more specifically, the left SLF-III would support the working memory phonological loop.[129] In the right hemisphere, damage to the SLF-I and II induced impairment in visuospatial working memory.[124] Diffusion MRI studies have shown converging results in different populations. Although most DTI studies do not provide details on the segments of the SLF, causal and correlation evidence indicate left lateralization for verbal and right lateralization for visual working memory.[124,130,157]

According to correlation evidence in large populations, the bilateral cingulum bundle, underlying connections among salience nodes that integrate the M-CIN,[77,87] would support working memory performance.[145,156,162]

Causal evidence have shown that the disruption of the FAT would affect verbal working memory performance, with results for the left[130]and the right hemisphere.[137] Diffusion MRI evidence supporting these findings is scarce, based on ROI analyses and provided results for both hemispheres.[153,164] Likewise, causal evidence indicates a potential support of the fronto-striatal tract to a network involved in verbal working memory in the left hemisphere, along with fronto-parietal connections and the FAT,[130]however, to our knowledge such association has not been reported in DTI studies.

Results from diffusion MRI studies included in this review suggest a potential support of projection tracts carrying cortico-subcortical connections to working memory, notably the EC and IC, along with the corpus callosum and fronto-parietal connections.[143,145,152,165] (Fig. 2; Supplementary Table 1)

Set-shifting

Causal evidence

Causal evidence indicated the involvement of the left SLF in performance on the TMT-B. According to lesion analyses of cholinergic lateral pathways in 106 patients after acute and chronic stroke, deficits were associated with damage to the left SLF.[167] Moreover, according to a case report, post-operative damage to the SLF induced significant deterioration in TMT-B shifting cost after surgical resection of a glioma located in the right hemisphere. Tractography analysis revealed damage to the SLF-III, the AF and to a lesser extent the middle longitudinal fasciculus and callosal fibers (tapetum); the SLF-I and II seemed relatively spared.[168] According to the authors, deterioration in set-shifting abilities resulted from disruption of a cognitive control network that spreads bilaterally in prefrontal but also cingular, parietal and temporal areas.[82] Indeed, the flexible switching between numbers and letters necessary for completing the TMT-B also relies on working memory and visuospatial attention[169,170]and, in previous studies, both the SLF-III and AF have been associated with visuospatial processing.[113,126]

Results from the study of Cochereau *et al.*[140] are slightly different. In this large cohort, long-lasting deficits on the TMT-B switch cost were prominently associated with post-surgical damage to the left SLF-II.

Correlation evidence

Several studies have shown contributions of the CC set-shifting abilities in clinical populations[171,172]and in healthy individuals across ages.[143,162,173,174]Other studies indicated associations between better DTI metrics in the SLF and better performance on different tasks assessing set-shifting, based on switch costs[171,175,176]and TMT-B completion time.[177,178]More precisely, in large samples of healthy adults, axial diffusivity in the left SLF-II strongly predicted shifting-specific ability.[174]Such associations were not observed for gray matter[174]and remained strong after accounting for global white matter.[176]

The anterior and posterior segments of the cingulum were strongly correlated with attention and flexible responses in large groups of healthy aging adults,[162,179]with no associations found with diffusivity or atrophy in cortical structures.[179]Also, the cingulum, along with the CC and the SLF, was associated with cognitive flexibility in persons with traumatic brain injury, suggesting its involvement in cognitive control networks.[171]

In two studies of healthy adults that used the TMT-B completion time[177]and switch cost[176]as assessment parameters, the integrity of the left and right IFOF strongly predicted performance, probably reflecting its implication in visually guided behavior.[180]

Regarding cortico-subcortical connections, results may vary depending on assessment methods and variables controlled. Analyses of clinical and healthy populations have shown associations between low performance on set-shifting paradigms and low integrity of cortico-subcortical loops with the pre-SMA and superior frontal gyrus, including clusters in the bilateral superior CR, including the IC and posterior TR.[181,182]In studies using the TMT-B completion time, better performance has been associated with better DTI parameters in the bilateral superior CR[178]; right[183]and bilateral IC.[184]However, in analyses of more than 300 healthy aging adults, correlations between the integrity of the left anterior TR and TMT-B completion time lost significance after controlling for processing speed by means of different tasks.[185]

Summary

Causal and correlation evidence have shown consistent associations between integrity of the SLF and set-shifting performance. Severe decline of set-shifting abilities was prominently associated with damage to the SLF-III and AF in the right hemisphere, but also the middle longitudinal fasciculus and callosal fibers reflecting network disruption.[168] In large populations, causal evidence indicate that the left SLF,[167]and more precisely the left SLF-II,[140]supported better performance. Convergent evidence from diffusion MRI studies in large populations agree with these findings, showing results for the left SLF[176] and left SLF-II.[174] Correlation studies exploring the CC showed frequent associations, especially with the genu[143,171,172,186]

To our knowledge, there is no causal evidence indicating associations between lesions in the cingulum bundle and decline in set-shifting abilities; however, according to correlation evidence it could be involved in networks supporting flexibility.[162,171]

Regarding cortico-thalamic and cortico-striatal connections, DTI studies indicate the support of the bilateral superior CR to flexible responses, within cortico-subcortical loops underlying cognitive control.[181,182](Fig. 2; Supplementary Table 1)

Inhibition

Causal evidence

Puglisi *et al.* assessed the feasibility of the Stroop task during awake surgery and showed that DES of specific white matter regions beneath the IFG and middle frontal gyrus, anterior to the insula and over the putamen induced task disruption, but patients made no errors in control tasks. In these patients, administration of the intraoperative Stroop task prevented executive deficits 3 months after resection.[187] In other analyses, the authors compared pre- and post-surgical cognitive outcomes of 29 patients undergoing resection of a right frontal glioma, by using DES, lesion-symptom mapping and diffusion tractography. DES of the anterior TR and fronto-striatal tracts produced errors during the Stroop test, but results from lesion analyses showed that inhibition was preserved in seven of eight patients with the inferior fronto-striatal tract spared.[188] However, overall differences before and after the surgery only approached significance and showed slower performance rather than errors. Moreover, all patients had lesions in the right hemisphere and were assessed only 1 month after surgery, which may be a short delay estimating long-lasting impairments.[189] In larger groups of patients, with lesions in the right and left hemisphere and at least 3 months after tumor resection, the Stroop interference index (i.e., time to complete the interference minus the color-naming condition) was predominantly associated with integrity of the SLF-II, to a lesser extent the SLF-III and weakly with fronto-striatal tracts, all left-lateralized.[140]

In the case report of Rutten *et al.* previously described,[137] DES to the right FAT induced errors in the Stroop task in a patient undergoing awake surgery for resection of a right frontal glioma; motor function was not disrupted.

Correlation evidence

Analyses of white matter associations with measures of inhibition (Stroop interference index, Tower of London) have shown widespread correlations in healthy and clinical populations. Several findings include the CC.[190,162,191–193] Regarding the fronto-parietal connectivity, studies using the Stroop and Go-No Go tasks have shown significant correlations between better performance and better DTI parameters (FA, axial diffusivity) in both the left and right SLF.[184,194–197]

Investigations of limbic-cortical networks and inhibition in small groups of people with psychiatric disorders suggested the involvement of the cingulum, showing DTI metrics of FA and MD associated with performance on the Stroop and Tower of Hanoi.[198,199]Convergent findings have been reported in other populations,[162,200,201]with its left posterior parts prominently associated with verbal rules (i.e., Stroop task) and its bilateral anterior parts sensitive to rule violations in the Tower of London task.[200]

Other tracts such as the fornix[184,202]and the uncinate fasciculus,[195,201]bilaterally, have been less consistently associated with performance on tasks assessing inhibition.

Results from studies of healthy and clinical populations using different tasks agree with descriptions of a right-lateralized fronto-subcortical network supporting inhibition[132,136]with convergent results for the right anterior TR.[203,202,197,191]In individuals with psychiatric conditions, executive impairment has been associated with abnormal activation in cortico-subcortical networks,[204–206]and low integrity of the right anterior IC.[204]In line with these findings, comprehensive analyses of neural correlates underlying cognitive control deficits have shown reduced FA in the right anterior limb of the IC associated with impaired Stroop interference index, along with abnormal activation of a right lateralized fronto-thalamo-cerebellar network.[207]Similar associations have been reported in other populations, concerning the bilateral anterior CR, bilateral anterior limb of the IC[190]and left EC.[208]

Summary

Results for inhibition points to a role for the CC, fronto-parietal and cortico-subcortical connections. Convergent findings from causal and correlation evidence using verbal tasks showed involvement of the left SLF.[140,194,195] More precisely, causal evidence in large populations showed results for the left SLF-II and III[140]

To our knowledge, there is no causal evidence showing the impact of altered integrity of the cingulum bundle in inhibition, but this has been supported by convergent findings from diffusion MRI analyses, using different tasks tapping inhibition.[198–201]Although other studies are needed to detail whether the cingulum bundle supports global or specific executive process, such associations would be in line with the role of the cingulate cortex in error detection[209,210] within the M-CIN network, engaged in salience detection and in maintaining task sets in demanding cognitive tasks.[77]

Causal evidence suggest the involvement of the right anterior TR in inhibition and showed changes in performance associated with damage to the right inferior fronto-striatal tract.[188] However, these results have not been confirmed in analyses of long-term executive impairment following tumor resection in large populations.[140]The diffusion MRI studies included in this review did not report associations between inhibition and integrity of the fronto-striatal tracts but several showed results for the right anterior TR.[191,197,202,203]

In line with the putative role of the right FAT in executive processes,[134] DES to the right FAT disrupted Stroop performance,[137] but this result has not been confirmed in post-lesional analyses of larger populations.[140] Diffusion MRI studies included in this review did not investigate such associations.(Fig. 2; Supplementary Table 1)

Discussion

This review aimed to identify white matter tracts consistently associated with performance on tasks assessing cognitive control abilities according to evidence from cognitive assessments during intraoperative brain mapping, studies using lesion-mapping and diffusion MRI. As expected, the CC was involved in all executive tasks, in different populations. Broadly and according to how executive functions are most frequently assessed,[44] results point to several white matter tracts, in particular those underlying fronto-parietal interactions,[98]within a network in which the SLF would be the main connection.

Causal and correlation evidence showed bilateral contributions of the SLF to global executive performance.[140,174,176,197]More precisely, the SLF was consistently involved in working memory,[124,129,130,147,150,151,153–159]assessed with verbal and visual tasks; the left SLF-II supported flexible responses[140,174]; causal and correlation evidence showed left lateralization for tasks assessing set-shifting and inhibition.[140,167,176]Moreover, convergent findings from diffusion MRI studies have shown significant contributions of the cingulum bundle to cognitive control.[162,171,179,198–201]To our knowledge, there is no causal evidence confirming findings for the cingulum. This can be partly explained by the scarcity of studies using executive tasks while performing brain mapping with DES and assessing associations between post-operative lesions and long-term executive abilities.[211–213]

Because subcortical structures modulate cortical responses,[136,142,214] the involvement of cortico-subcortical connections in cognitive control functions is expected. Several analyses indicate a role for cortico-thalamic and cortico-striatal white matter, especially for the right anterior TR in tasks assessing inhibition.[188,191,197,202,203]Other studies, including causal evidence showed the involvement of the FAT and fronto-striatal tracts[130,137,140,164,188] in performance on executive tasks. However, only one study[140] exploring associations with the FAT and fronto-striatal tracts used whole-brain analyses and comprehensive executive assessment, which allows for comparing possible associations. Whether these connections are crucial for executive functions needs further research.

In the next subsections, we discuss more in detail the results from this review for each white matter tract and their specificity regarding other findings about their functional roles.

The corpus callosum

The CC is the largest commissural tract in the brain connecting left and right hemispheres. It ensures interhemispheric transfer and integration of motor, sensory and cognitive information between homologous regions. It would also regulate homologous regions via an excitatory and inhibitory process, for optimal information processing. Its central importance in cognition has been largely demonstrated (i.e., in individuals with traumatic brain injury, the high vulnerability of the CC to long-term axonal injury was found associated with diverse cognitive deficits and with a significant impact on clinical outcomes).[215–217]Different subdivisions of the CC have been described according to topographical organization, including the genu, connecting symmetrical dorsolateral prefrontal regions; the body, containing fibers connecting the premotor and precentral frontal cortex; and the splenium, connecting occipital-temporal regions.[123] Studies of patients with partial callosotomy showed functional differences of these subcomponents, its posterior parts supporting visual, auditory and somatosensory information and anterior parts supporting cognitive processes such as attention and executive functions.[218] As expected, studies included in this review have shown consistent support of the CC to all executive processes, notably the CC genu in working memory. Anterior CC parts such as the genu are thought to be involved in executive functions given the numerous projections within regions such as the left and right dorsolateral PFC, IFG and superior frontal gyrus, playing a critical role in such abilities.[219] The unspecific but essential role of the CC has been further confirmed in DTI studies showing independent contributions of the CC to executive performance and global cognition.[162,220–222]

Consistent involvement of the SLF in executive functions

Causal evidence from studies using DES and post-lesion cognitive assessment included in this review suggests that the SLF is a key white matter structure subserving executive processes [124,129,130,140,167,168] The SLF is a major association tract connecting lateral frontal, parietal and temporal cortical regions. Descriptions identify three[223,224]and others four segments[225] and functional differentiations. The SLF-I (dorsal part) connects parts of the superior parietal lobule with the superior frontal lobe, extending from the medial and dorsal parietal cortex to the dorsal part of the premotor and prefrontal cortices. The SLF-II (middle part) connects regions around the intraparietal sulcus to regions in the superior and middle frontal gyrus including the frontal eye fields, extending from the caudal part of the inferior parietal lobule to the dorsal premotor and prefrontal cortices. The SLF-III (ventral part) connects the inferior parietal lobule to the IFG, extending from the rostral inferior parietal lobule to the ventral part of the premotor and prefrontal cortices. The fourth subcomponent, the SLF-temporoparietal segment (SLF-tp), connects temporal and parietal cortices, running posteriorly from the inferior parietal lobe to the posterior temporal lobe.[223,225]A number of studies in the past decade have indicated the support of SLF to a wide array of cognitive processes, from visual attention to language and complex cognitive control processes.[95,110,113,126–128,226]

In the right hemisphere, three branches of the SLF underlie a visuospatial network with distinct functional roles.[128] The SLF-I is thought to support goal-directed spatial attention via a dorsal-mesial pathway,[110]whereas the SLF-III would support automatic capture of salient stimuli via a ventral pathway.[128] The SLF-II would integrate information from the SLF-I and III, therefore mediating interaction between dorsal and ventral attention systems.[128,223] Damage to this segment in the right hemisphere induced left spatial neglect.[113,125]Beyond visuospatial attention, the right SLF-II and III would also be involved in motor aspects of attention (i.e., visuomotor speed and movement trajectory control) and bilaterally with cognitive aspects of motor function.[225,227]In comprehensive analyses combining tractography and a meta-analytic approach to cluster fronto-parietal functions, the SLF-I was the main tract associated with spatial/motor clusters (e.g., saccades, voluntary oriented attention) and the SLF-III, with non-spatial/motor clusters,(e.g., verbal working memory, decision making); the SLF-II was associated with both.[226] In line with these descriptions, results from causal evidence included in this review have shown the support of the right SLF-I and II to visuospatial working memory[124] and the left SLF-I to verbal working memory.[130]Also, DES of the left SLF-III produced selective disruption of digit spans performance, eliciting order rather than item errors. A similar disruption occurred when the supramarginal gyrus was stimulated, leading to the hypothesis of its role in the phonological loop by transferring order information from the phonological store to Broca’s area.[129] The role of the SLF and its different branches in language processes has been demonstrated.[95] The SLF-III is thought to support phonological and articulatory processes according to causal evidence,[95,228] and results of Papagno *et al.*[129] suggest a specific functional role of the SLF-III in verbal working memory tasks. DTI studies have shown similar associations between the integrity of the left SLF and performance on different verbal working memory tasks.[147,153,159] The SLF is indeed a major connection underlying areas of activation during working memory tasks regardless of their specific aspects and features, forming a "core" working memory network, including clusters in frontal, parietal and insular cortices.[88]

According to results from causal and correlation evidence in large populations, the left SLF-II would play a prominent role in flexible responses.[140,174] Strong evidence indicates a role for the left SLF-II and III in performance of tasks assessing flexibility and inhibition, according to analyses of resection cavities and disconnection probability in a large cohort of patients with brain tumor, showing long-lasting impairment on the Stroop task and TMT-B switch cost. The left SLF-II was strongly correlated with both measures and with global executive performance.[140] Causal evidence also showed that damage to the SLF-II, SLF-III and the AF disrupted performance on the TMT-B, which assesses attentional flexibility with significant visuospatial attentional demands.[140,168]These were located in the right hemisphere in the study of Mandonnet *et al.*,[168] thus reflecting recruitment of visuospatial attention networks. Indeed, the role of the fronto-parietal white matter in maintaining executive function has been recently demonstrated in a large study exploring the impact of cardiovascular risk factors on cognition.[98]

Results from this review showed involvement of the SLF in all executive tasks, regardless the parameters used to interpret performance across studies. Given that attentional processes are essential for executive functions, the SLF is likely crucial because it supports the integration of information within low top-down, visual, goal-oriented attention[75,128,227]and cognitive control networks (i.e., the D-FPN and L-FPN networks)[75,77]that is needed to goal-oriented behavior.

Contributions of the cingulum bundle to executive functions

Despite no causal evidence for the cingulum to our knowledge, it has been associated executive performance in several DTI studies of large populations.[145,162,179] Indeed, according to a recent synthesis focusing in other methods, frequent correlations have been reported between executive assessments and integrity of the cingulum.[100]In detailed analyses of executive performance, higher FA in the cingulum bundle independently contributed to better performance on the three executive domains.[162] This complex white matter tract comprises short and long fibers that extend above the CC and connect the cingulate cortex with different cortical and subcortical regions, some belonging to the limbic system. Some of its fibers connect the anterior and lateral dorsal thalamic nuclei, dorsolateral PFC and insula. Others connect parts of the temporal lobes, such as subicular cortices, parahippocampal cortices and amygdala.[161] Different segments of the cingulum have been described to improve the understanding of its potential underlying functions, from two ("dorsal" and "ventral") to five subdivisions (subgenual, anterior, midcingulate, retrosplenial, and parahippocampal or temporal).[161,229,230] Via a large fronto-parietal connectivity within the cingulum, all of its components likely support interactions between working memory and attentional resource allocation.[161] Results from this review suggest the involvement of its bilateral anterior, posterior and left parahippocampal segments in verbal working memory.[145,156] Several studies have suggested its support of flexible responses and inhibition abilities,[162,171,179,198,199,201]consistent with the previously described role of the anterior cingulate cortex in error detection.[209,210]Moreover, the anterior/superior cingulum is connected to the central precuneus, which has been recently shown to support set-shifting[231] and, more dorsally, is likely a D-FPN node.[77] By supporting connections among key network nodes of salience detection,[87] the cingulum bundle is probably an important connection underlying interactions within the L-FPN and M-CIN networks.[77] Other studies are needed to increase knowledge about the weight and specificity of cingulum contributions to executive functions, and describe possible functional differentiations between its different segments.

The FAT and its putative role in cognitive control

According to direct in vivo evidence, the right FAT would be involved in executive functions, because DES of this white matter tract in the right hemisphere disrupted the manipulation of verbal information in working memory and inhibition of prepotent responses, whereas the performance of digit spans forward remained normal.[137]Also, lesion analyses of large populations have shown results for verbal working memory,[130]moderate correlations between global executive performance but also verbal fluency, and damage to the FAT in the left hemisphere.[140]Regarding DTI studies, there is limited evidence: two studies included in this review have suggested the involvement of the FAT in verbal working memory,[153,164] in one of them bilaterally.[153] The FAT was first detected in a study exploring brain structures involved in cognitive control. Aron *et al.*[132] identified a white matter structure linking the inferior frontal cortex and the pre-SMA to the subthalamic nucleus, underlying the connectivity of a frontal-subcortical network for response control. Given its connectivity with the IFG and cases of SMA syndrome (reduction of spontaneous movement and speech function) after tumor resections,[96] much of the research on the FAT has been related to language function, showing its support of speech and language initiation, especially in the left hemisphere.[133,135,232]Recently, detailed analyses showed a prominent role of the FAT in motor aspects of the language.[233]However, such associations are not restricted to the left hemisphere: some studies indicate the involvement of the right FAT in stuttering and verbal fluency.[234,235]

A role for the right FAT in executive functions has been hypothesized.[134] The pre-SMA and SMA subserve motor control, stopping behaviors and more specifically, conflict resolution between competing action plans[68,236,237] and have been identified as key nodes for verbal and non verbal working memory.[88,138,139] These structures and the right IGF would interact during context monitoring,[46,238]and the FAT would support these interactions within a broad cortico-basal ganglia-thalamic-cerebellar circuit involved in action control.[134,239]In line with this hypothesis, causal[137,140]and correlation evidence[153,164]showed its association with executive, goal-directed processes during verbal tasks. The FAT underlies connections among key nodes engaged in executive processes[87,88,239]; however, the current literature does not allow for inferences about the need or specificity of its role in such processes, that is, whether the FAT would support broad cognitive control processes or if it would have an indirect role in executive performance via the control of verbal responses.

Cortico-striatal and cortico-thalamic connections

Several studies showed associations between executive functions and the integrity of tracts supporting of cortico-striatal and cortico-thalamic circuits, involved in the L-FPN and M-CIN.[77] DES results from Puglisi *et al.*[188] differ from post-surgical assessments, in terms of tracts involved and nature of the post-surgery changes in performance. DES of the right anterior TR and right inferior fronto-striatal tracts elicited mainly errors rather than slowing during performance of the Stroop task, but conclusions of lesion analyses in a subgroup of patients describe a subtle slowing of performance only in those with the fronto-striatal tract resected. Other results indicate a role for the fronto-striatal tracts in verbal working memory, along with the FAT and the SLF[130] but also in global executive function in the left hemisphere.[140] According to a recent study using voxel-based lesion-symptom mapping in 36 patients who underwent glioma resection in the right hemisphere, simultaneous damage of the middle cingulate cortex and the fronto-striatal tract caused selective visual attention deficits, indicating that it could support attention control.[240]Nonetheless, the specificity of such associations remains unclear. Damage to the fronto-striatal tract may affect cognitive control functions because it connects key nodes supporting these processes; moreover, it has been involved in motor inhibition and language initiation.[102,135,140]Analyses in large populations suggest that, in the left hemisphere, its role is predominantly related to the verbal demands of executive tasks.[140] Concerning the right anterior TR, DTI studies have shown converging findings suggesting its involvement in performance on tasks assessing response inhibition.[8–11]This is in line with a voxel-based lesion-symptom mapping showing that lacunar lesions located in the SLF and anterior TR were associated with poor global executive function,[241]reflecting disruption of large-scale FPN-subcortical interactions. Moreover, the integrity of the right SLF-II and left anterior TR supported better Common EF[174]in analyses of the neural substrates underlying the unity/diversity model. The question of whether the anterior thalamic radiations and fronto-striatal tracts are necessary for normal cognitive control needs further investigation, but these convergent findings provide strong evidence of their implication in executive functions.

Other results from DTI studies in large populations suggest that the EC, IC, CR are involved in cognitive control processes[143,145,152,165,178,181,182,190,207,208]along with fronto-parietal connections and the CC. Some studies showed contributions of these fibers to global executive function[208,242] and in others, changes in activations of cortico-subcortical networks during task performance supported such associations.[165,207] Collectively, causal and correlation evidence agree with research describing thalamic modulation of functional connectivity across cortical regions, and the role of thalamic nuclei in cognitive processes such as attention, behavioral flexibility and more broadly, attentional control.[67,243]As mentioned above, more than being relays of sensorial information, basal ganglia structures have been identified as key nodes in neural models of executive functions,[136]supporting cognitive control within the L-FPN and the M-CIN networks.[77]

Taken together, results from studies included in this review indicate the essential role of the structural connectivity underlying the D-FPN, L-FPN and M-CIN networks in executive functions. These networks very flexibly support a wide array of cognitive processes such as attentional control, selection and salience detection.[77,244]Complex responses emerge from the interactions among these systems and widespread hub regions, which in turn mediate the integration of low-level sensorial, motor and cognitive processes generated in other brain regions.[76,77]Among them, the L-FPN, originally described as the multiple-demand system,[81,82]is thought to be paramount for executive responses.[77]The central role of white matter underlying this network has been corroborated in a recent study showing that lesions to the subcortical connectivity of the multiple-demand system in the left hemisphere were associated with greater impairments in tasks assessing cognitive control.[99]At the same time, the complex interconnectivity within the PFC reflects some degree of specialization in small areas. Indeed, executive processes involve the integration of different levels of information processing and dynamic network reconfiguration in a context-sensitive manner,[244] implying that parallel to these domain-general structures, the information processing of other task features and sensorial demands rely on several other white matter tracts. Accordingly, results from some DTI studies included in this review indicated the involvement of white matter tracts that were previously associated with sensorial, language or semantic processing in executive functions. For example, the uncinate fasciculus, playing a central role in language,[95,245] was among the tracts associated with performance on executive tasks with verbal demands.[195]Also supporting language, the AF is associated with the phonological loop[95,96,246]and, according to causal evidence, disconnection of its right fronto-parietal segment significantly predicted spatial neglect.[113] In line with these findings, severe decline in set-shifting abilities assessed with the TMT-B, involved damage to the AF,[168]whereas DTI studies showed its associations with verbal working memory.[147,150]Moreover, the IFOF, one of the major association tracts mediating visuospatial awareness[96,125,247,248];language,[95]including lexical and semantic processing,[96,249]but also non-verbal semantic cognition,[250] significantly predicted performance on tasks requiring visuospatial processing.[176,177,251] In a study using the TMT-B completion time to measure set-shifting performance, the right IFOF remained the single predictor after controlling for age.[177]These results should be interpreted in light of the diversity of cognitive processes involved in tasks assessing executive functions.[44]Findings showing the involvement of multiple tracts does not necessarily imply the need for all of them for a given executive process, but show that these structures participate in the integration of information from multiple networks recruited during the performance of a given cognitive task, according to its demands.

There are limitations to this review. Although the cognitive tasks were included in different sections (working memory, shifting, inhibition) according to their common use in clinical practice and research, such presentation of results could hinder the interpretations concerning other cognitive processes required for performing executive tasks. It is important to bear in mind that, although in theory there are separable executive constructs, executive processes interact with each other and tasks tap executive and non-executive processes (i.e., executive tasks are generally used as a proxy for one particular construct but may capture variance associated with several constructs).[40] For example, the integrity of projection fibers have been correlated with parameters of tasks or performance that also tap working memory capacity,[170,252]such as the TMT-B completion time,[183,184] and the Tower of London.[202]However, the objective of this review was to identify associations with tasks that are commonly used in the literature to assess cognitive control abilities. Considering the multifactorial aspects of executive tasks and the multiple functional roles described for some white matter tracts, overlapping is expected and the results of this review underline such aspect. Moreover, results were presented regarding the parameters used in the studies to interpret performance and other cognitive processes potentially involved. Other limits relate to technical aspects of each method used for the study of white matter and the availability of causal evidence. At the neural level, performance of executive tasks relies on the activity of specific brain networks and also the interactions among these networks.[253,254]Accordingly, the DTI studies selected in this review have shown different groups of white matter tracts associated with executive tasks. Our objective was to highlight consistent associations, but these are certainly more complex because a single tract can be correlated with multiple cognitive tasks and behaviors.[100] However, highlighting consistent findings may contribute to identifying not only tracts subserving multiple functions, but also those playing a less essential role that can be compensated for in case of a lesion.[255] Concerning diffusion weighted MRI studies, the sensitivity of the DTI metrics used as parameters for white matter integrity may be limited and hinder the identification of the spatial limits of white matter structures, especially white matter tracts containing “kissing” or crossing fibers.[117101] Metrics derived from DKI seem to be more sensitive to changes in fiber diffusivity[117,119]; however, DKI is a time-consuming imaging technique mostly restricted to study protocols and not used in routine clinical practice. Only two studies included in this review used DKI to assess white matter tracts associated with specific executive tasks.[149,158] Nonetheless, several well-controlled studies including large samples have shown convergent findings, (Supplementary Table 1) thus indicating the tracts underlying the connectivity of well-described executive networks. Finally, several DTI studies contained no precise information on tract segments, although some have been described, such as the SLF[123,160,223]and the cingulum bundle.[161,229,230] This information is essential especially for complex and long connections that may induce specific deficits when damaged at precise locations.[96]Concerning causal evidence, some conclusions remain limited because of the scarce data from lesion analyses and DES results from the neuro-oncology field, regarding executive functions.[211,213]

Conclusions: clinical implications and perspectives

Evidence shows that executive functions are supported by white matter tracts connecting widespread brain regions and those underlying the connectivity of fronto-parietal networks may be necessary for these complex cognitive processes. Research on the involvement of white matter tracts in cognition is of paramount interest, especially for the neuro-oncology field. DES during awake surgery has considerably improved the quality of tumor resection while preserving cognitive functions, even in highly eloquent regions. Understanding the role of some specific white matter bundles allows for the optimizing of sub-cortical mapping and tumor resection while limiting post-surgical sequelae.[96,101]Indeed, compensation mechanisms are possible upon white matter sparing; otherwise, spatial communication and synchronization among potentially compensating neural networks are compromised.[29,32]However, although the intraoperative mapping of white matter tracts involved in executive functions has started only recently and certainly needs to be optimized, assessing its effective benefits for patients in terms of onco-functional balance remains (i.e., the best trade-off between resecting the tumor and sparing functions).[256]To the best of our knowledge, only a small number of large-scale neuropsychological studies has comprehensively assessed executive functions in a longitudinal setting (i.e., before and after surgery) in an attempt to characterize levels of recovery.[213]Because tumors, especially lower-grade glioma, trigger massive compensatory mechanisms,[32]such kinds of studies are essential to determine whether executive functions recover after surgery and, if not enough, which kinds of behavioral tasks should used to reduce the likelihood of post-operative impairments in patient-specific manner.[257]These studies are also important to determine the extent to which tracts supporting executive functions are compensable when invaded by the tumor, a key issue for the surgical planning.

In many cases, radiotherapy is an essential treatment for brain tumors but was found associated with radiation-induced cognitive decline after white matter damage in a subpopulation of long-term survivors.[258]Several DTI studies exploring white matter in patients with brain tumor revealed early microstructural changes after radiotherapy, which progressed over time and were dose-dependent.[259,260]Among these structures, the cingulum bundle was especially sensitive to radiation-induced demyelination in white matter,[261] so damage of this tract could participate in the long-term cognitive decline observed in these patients.[6]Knowledge of the role of white matter tracts can contribute to the development of radiotherapy techniques[262] allowing to spare functionally important white matter tracts, which seems a promising strategy to limit severe cognitive disability in patients with brain tumor.

Acknowledgements

We received logistic and administrative support from the C.R.N.O. (Centre de Recherche en Neuro-Oncologie) and the SiRIC (Site de Recherche Intégrée sur le Cancer) CURAMUS (INCa-DGOS-Inserm_12560), to accomplish this work.

Funding

No funding was received towards this work.

Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

References

1. Geschwind N. Disconnexion syndromes in animals and man. *Brain*. 1965;88(2):237-237. doi:10.1093/brain/88.2.237
2. Mesulam M. From sensation to cognition. *Brain*. 1998;121(6):1013-1052. doi:10.1093/brain/121.6.1013
3. Mesulam MM. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Annals of Neurology*. 1990;28(5):597-613. doi:10.1002/ana.410280502
4. Omuro AMP, Ben-Porat LS, Panageas KS, et al. Delayed Neurotoxicity in Primary Central Nervous System Lymphoma. *Archives of Neurology*. 2005;62(10). doi:10.1001/archneur.62.10.1595
5. Filley CM, Fields RD. White matter and cognition: making the connection. *Journal of Neurophysiology*. 2016;116(5):2093-2104. doi:10.1152/jn.00221.2016
6. Bompaire F, Lahutte M, Buffat S, et al. New insights in radiation-induced leukoencephalopathy: a prospective cross-sectional study. *Support Care Cancer*. 2018;26(12):4217-4226. doi:10.1007/s00520-018-4296-9
7. Catani M, Dell'Acqua F, Bizzi A, et al. Beyond cortical localization in clinico-anatomical correlation. *Cortex*. 2012;48(10):1262-1287. doi:10.1016/j.cortex.2012.07.001
8. Park HJ, Friston K. Structural and Functional Brain Networks: From Connections to Cognition. *Science*. 2013;342(6158):1238411-1238411. doi:10.1126/science.1238411
9. Sporns O, Tononi G, Kötter R. The Human Connectome: A Structural Description of the Human Brain. *PLoS Computational Biology*.2005;1(4):e42. doi:10.1371/journal.pcbi.0010042
10. Bassett DS, Bullmore ET. Human brain networks in health and disease. *Curr Opin Neurol*. 2009;22(4):340-347. doi:10.1097/WCO.0b013e32832d93dd
11. Herbet G, Duffau H. Revisiting the Functional Anatomy of the Human Brain: Toward a Meta-Networking Theory of Cerebral Functions. *Physiological Reviews*. 2020;100(3):1181-1228. doi:10.1152/physrev.00033.2019

12. Thiebaut de Schotten M, Forkel SJ. The emergent properties of the connected brain. *Science*. 2022;378(6619):505-510. doi:10.1126/science.abq2591

13. Filley CM. White Matter: Organization and Functional Relevance. *Neuropsychology Review*. 2010;20(2):158-173. doi:10.1007/s11065-010-9127-9

14. Catani M. From hodology to function. *Brain*. 2007;130(3):602-605. doi:10.1093/brain/awm008

15. Azouvi P, Arnould A, Dromer E, Vallat-Azouvi C. Neuropsychology of traumatic brain injury: An expert overview. *Revue Neurologique*. 2017;173(7-8):461-472. doi:10.1016/j.neurol.2017.07.006

16. Fagerholm ED, Hellyer PJ, Scott G, Leech R, Sharp DJ. Disconnection of network hubs and cognitive impairment after traumatic brain injury. *Brain*. 2015;138(6):1696-1709. doi:10.1093/brain/awv075

17. Hulkower MB, Poliak DB, Rosenbaum SB, Zimmerman ME, Lipton ML. A Decade of DTI in Traumatic Brain Injury: 10 Years and 100 Articles Later. *American Journal of Neuroradiology*. 2013;34(11):2064-2074. doi:10.3174/ajnr.A3395

18. Dineen RA, Vilisaar J, Hlinka J, et al. Disconnection as a mechanism for cognitive dysfunction in multiple sclerosis. *Brain*. 2009;132(1):239-249. doi:10.1093/brain/awn275

19. Pagani E, Rocca MA, De Meo E, et al. Structural connectivity in multiple sclerosis and modeling of disconnection. *Mult Scler*. 2020;26(2):220-232. doi:10.1177/1352458518820759

20. Lin L, Xue Y, Duan Q, et al. Microstructural White Matter Abnormalities and Cognitive Dysfunction in Subcortical Ischemic Vascular Disease: an Atlas-Based Diffusion Tensor Analysis Study. *J Mol Neurosci*. 2015;56(2):363-370. doi:10.1007/s12031-015-0550-5

21. Cole MW, Repovš G, Anticevic A. The Frontoparietal Control System: A Central Role in Mental Health. *The Neuroscientist.* 2014;20(6):652-664. doi:10.1177/1073858414525995

22. Snyder HR, Miyake A, Hankin BL. Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. *Front Psychol*. 2015;6. doi:10.3389/fpsyg.2015.00328

23. Madden DJ, Bennett IJ, Burzynska A, Potter GG, Chen N kuei, Song AW. Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*. 2012;1822(3):386-400. doi:10.1016/j.bbadis.2011.08.003

24. Bennett IJ, Madden DJ. Disconnected aging: Cerebral white matter integrity and age-related differences in cognition. *Neuroscience*. 2014;276:187-205. doi:10.1016/j.neuroscience.2013.11.026

25. Charlton RA, Barrick TR, McIntyre DJ, et al. White matter damage on diffusion tensor imaging correlates with age-related cognitive decline. *Neurology*. 2006;66(2):217-222. doi:10.1212/01.wnl.0000194256.15247.83

26. Coelho A, Fernandes HM, Magalhães R, et al. Signatures of white-matter microstructure degradation during aging and its association with cognitive status. *Sci Rep*. 2021;11(1):4517. doi:10.1038/s41598-021-83983-7

27. Hinton KE, Lahey BB, Villalta-Gil V, et al. Right Fronto-Subcortical White Matter Microstructure Predicts Cognitive Control Ability on the Go/No-go Task in a Community Sample. *Frontiers in Human Neuroscience*. 2018;12. doi:10.3389/fnhum.2018.00127

28. Duffau H. Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. *The Lancet Neurology*. 2005;4(8):476-486. doi:10.1016/S1474-4422(05)70140-X

29. Herbet G, Maheu M, Costi E, Lafargue G, Duffau H. Mapping neuroplastic potential in brain-damaged patients. *Brain*. 2016;139(3):829-844. doi:10.1093/brain/awv394

30. Desmurget M, Bonnetblanc F, Duffau H. Contrasting acute and slow-growing lesions: a new door to brain plasticity. *Brain*. 2007;130(4):898-914. doi:10.1093/brain/awl300

31. Desmurget M, Song Z, Mottolese C, Sirigu A. Re-establishing the merits of electrical brain stimulation. *Trends in Cognitive Sciences*. 2013;17(9):442-449. doi:10.1016/j.tics.2013.07.002

32. Duffau H. Hodotopy, neuroplasticity and diffuse gliomas. *Neurochirurgie*. 2017;63(3):259-265. doi:10.1016/j.neuchi.2016.12.001

33. Filley CM. *The Behavioral Neurology of White Matter*. 2nd ed. Oxford University Press; 2012.

34. Wallin A, Román GC, Esiri M, et al. Update on Vascular Cognitive Impairment Associated with Subcortical Small-Vessel Disease2. Perry G, Avila J, Tabaton M, Zhu X, eds. *Journal of Alzheimer's Disease*. 2018;62(3):1417-1441. doi:10.3233/JAD-170803

35. Benedict RHB, Cookfair D, Gavett R, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J Int Neuropsychol Soc*. 2006;12(4):549-558. doi:10.1017/s1355617706060723

36. Lezak MD, ed. *Neuropsychological Assessment*. 5th ed. Oxford University Press; 2012.

37. Godefroy O. Fonctions de contrôle frontales et syndromes dysexécutifs : quelles délimitations et quelles avancées ? *Revue de neuropsychologie*. 2009;1(1):12-. doi:10.3917/rne.011.0012

38. Hofmann W, Schmeichel BJ, Baddeley AD. Executive functions and self-regulation. *Trends in Cognitive Sciences*. 2012;16(3):174-180. doi:10.1016/j.tics.2012.01.006

39. Diamond A. Executive Functions. *Annual Review of Psychology*. 2013;64(1):135-168. doi:10.1146/annurev-psych-113011-143750

40. Friedman NP, Miyake A. Unity and diversity of executive functions: Individual differences as a window on cognitive structure. *Cortex*. 2017;86:186-204. doi:10.1016/j.cortex.2016.04.023

41. Kane MJ, Bleckley MK, Conway AR, Engle RW. A controlled-attention view of working-memory capacity. *J Exp Psychol Gen*. 2001;130(2):169-183.

42. McCabe DP, Roediger HL, McDaniel MA, Balota DA, Hambrick DZ. The relationship between working memory capacity and executive functioning: Evidence for a common executive attention construct. *Neuropsychology*. 2010;24(2):222-243. doi:10.1037/a0017619

43. Posner M, Digirolamo G. Executive attention: Conflict, target detection, and cognitive control,. *The Attentive Brain*. Published online January 1, 1998.

44. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The Unity and

Diversity of Executive Functions and Their Contributions to Complex “Frontal Lobe” Tasks: A Latent Variable Analysis. *Cognitive Psychology*. 2000;41(1):49-100. doi:10.1006/cogp.1999.0734

45. Miyake A, Friedman NP. The Nature and Organization of Individual Differences in Executive Functions: Four General Conclusions. *Current Directions in Psychological Science*. 2012;21(1):8-14. doi:10.1177/0963721411429458

46. Chatham CH, Claus ED, Kim A, Curran T, Banich MT, Munakata Y. Cognitive Control Reflects Context Monitoring, Not Motoric Stopping, in Response Inhibition. Gilbert S, ed. *PLoS ONE*. 2012;7(2):e31546. doi:10.1371/journal.pone.0031546

47. Hampshire A, Sharp DJ. Contrasting network and modular perspectives on inhibitory control. *Trends in Cognitive Sciences*. 2015;19(8):445-452. doi:10.1016/j.tics.2015.06.006

48. Norman DA, Shallice T. Attention to action: Willed and automatic control of behavior. In: *Consciousness and Self-Regulation: Advances in Research and Theory Volume 4*. Springer; 1986:1-18.

49. Stuss DT, Alexander MP. Executive functions and the frontal lobes: a conceptual view. *Psychological research*. 2000;63(3-4):289-298.

50. Burgess PW. Theory and methodology in executive function research. In: *Methodology of Frontal and Executive Function*. Routledge; 2004:87-121.

51. Braver TS. The variable nature of cognitive control: a dual mechanisms framework. *Trends in Cognitive Sciences*. 2012;16(2):106-113. doi:10.1016/j.tics.2011.12.010

52. Baddeley A. Working Memory: Theories, Models, and Controversies. *Annual Review of Psychology*. 2012;63(1):1-29. doi:10.1146/annurev-psych-120710-100422

53. D’Esposito M, Postle BR. The Cognitive Neuroscience of Working Memory. *Annu Rev Psychol*. 2015;66(1):115-142. doi:10.1146/annurev-psych-010814-015031

54. Baddeley A, Hitch G. Working Memory. In: *Psychology of Learning and Motivation*. Vol 8. Elsevier; 1974:47-89. doi:10.1016/S0079-7421(08)60452-1

55. Baddeley AD, Logie RH. Working Memory: The Multiple-Component Model. In: Miyake

A, Shah P, eds. *Models of Working Memory*. 1st ed. Cambridge University Press; 1999:28-61. doi:10.1017/CBO9781139174909.005

56. Wechsler D. Wechsler Adult Intelligence Scale--Fourth Edition. Published online November 12, 2012. doi:10.1037/t15169-000

57. Kirchner WK. Age differences in short-term retention of rapidly changing information. *Journal of Experimental Psychology*. 1958;55(4):352-358. doi:10.1037/h0043688

58. Dajani DR, Uddin LQ. Demystifying cognitive flexibility: Implications for clinical and developmental neuroscience. *Trends in Neurosciences*. 2015;38(9):571-578. doi:10.1016/j.tins.2015.07.003

59. Jamadar SD, Thienel R, Karayanidis F. Task Switching Processes. In: *Brain Mapping*. Elsevier; 2015:327-335. doi:10.1016/B978-0-12-397025-1.00250-5

60. Uddin LQ. Cognitive and behavioural flexibility: neural mechanisms and clinical considerations. *Nat Rev Neurosci*. 2021;22(3):167-179. doi:10.1038/s41583-021-00428-w

61. Bowie CR, Harvey PD. Administration and interpretation of the Trail Making Test. *Nat Protoc*. 2006;1(5):2277-2281. doi:10.1038/nprot.2006.390

62. Nelson HE. A Modified Card Sorting Test Sensitive to Frontal Lobe Defects. *Cortex*. 1976;12(4):313-324. doi:10.1016/S0010-9452(76)80035-4

63. Aron AR. The Neural Basis of Inhibition in Cognitive Control. *Neuroscientist*. 2007;13(3):214-228. doi:10.1177/1073858407299288

64. Friedman NP, Miyake A. The Relations Among Inhibition and Interference Control Functions: A Latent-Variable Analysis. *Journal of Experimental Psychology: General*. 2004;133(1):101-135. doi:10.1037/0096-3445.133.1.101

65. Anderson MC, Green C. Suppressing unwanted memories by executive control. *Nature*. 2001;410(6826):366-369. doi:10.1038/35066572

66. Conway MA. Repression revisited. *Nature*. 2001;410(6826):319-320. doi:10.1038/35066672

67. Jahanshahi M, Obeso I, Rothwell JC, Obeso JA. A fronto–striato–subthalamic–pallidal network for goal-directed and habitual inhibition. *Nat Rev Neurosci*. 2015;16(12):719-732.

doi:10.1038/nrn4038

68. Zhang R, Geng X, Lee TMC. Large-scale functional neural network correlates of response inhibition: an fMRI meta-analysis. *Brain Struct Funct*. 2017;222(9):3973-3990. doi:10.1007/s00429-017-1443-x

69. Stroop JR. Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*. 1935;18(6):643-662. doi:10.1037/h0054651

70. Shallice T. Specific impairments of planning. *Philos Trans R Soc Lond B Biol Sci*. 1982;298(1089):199-209. doi:10.1098/rstb.1982.0082

71. Drewe EA. Go - no go learning after frontal lobe lesions in humans. *Cortex*. 1975;11(1):8-16. doi:10.1016/s0010-9452(75)80015-3

72. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *Journal of Neuroscience*. 2007;27(9):2349-2356. doi:10.1523/JNEUROSCI.5587-06.2007

73. Damoiseaux JS, Rombouts SARB, Barkhof F, et al. Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences*. 2006;103(37):13848-13853. doi:10.1073/pnas.0601417103

74. Fox MD, Corbetta M, Snyder AZ, Vincent JL, Raichle ME. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proceedings of the National Academy of Sciences*. 2006;103(26):10046-10051. doi:10.1073/pnas.0604187103

75. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*. 2002;3(3):201-215. doi:10.1038/nrn755

76. Gratton C, Sun H, Petersen SE. Control networks and hubs. *Psychophysiol*. 2018;55(3):e13032. doi:10.1111/psyp.13032

77. Uddin LQ, Yeo BTT, Spreng RN. Towards a Universal Taxonomy of Macro-scale Functional Human Brain Networks. *Brain Topogr*. 2019;32(6):926-942. doi:10.1007/s10548-019-00744-6

78. Niendam TA, Laird AR, Ray KL, Dean YM, Glahn DC, Carter CS. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cogn*

Affect Behav Neurosci. 2012;12(2):241-268. doi:10.3758/s13415-011-0083-5

79. Gordon EM, Laumann TO, Gilmore AW, et al. Precision Functional Mapping of Individual Human Brains. *Neuron*. 2017;95(4):791-807.e7. doi:10.1016/j.neuron.2017.07.011

80. Yeo BT, Krienen FM, Sepulcre J, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*. 2011;106(3):1125-1165. doi:10.1152/jn.00338.2011

81. Fedorenko E, Duncan J, Kanwisher N. Broad domain generality in focal regions of frontal and parietal cortex. *Proceedings of the National Academy of Sciences*. 2013;110(41):16616-16621. doi:10.1073/pnas.1315235110

82. Duncan J. The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends in Cognitive Sciences*. 2010;14(4):172-179. doi:10.1016/j.tics.2010.01.004

83. Rodríguez-Nieto G, Seer C, Sidlauskaite J, et al. Inhibition, Shifting and Updating: Inter and intra-domain commonalities and differences from an executive functions activation likelihood estimation meta-analysis. *NeuroImage*. 2022;264:119665. doi:10.1016/j.neuroimage.2022.119665

84. Zhang Z, Peng P, Eickhoff SB, Lin X, Zhang D, Wang Y. Neural substrates of the executive function construct, age-related changes, and task materials in adolescents and adults: ALE meta-analyses of 408 fMRI studies. *Developmental Science*. 2021;24(6). doi:10.1111/desc.13111

85. Collette F, Van der Linden M, Laureys S, et al. Exploring the unity and diversity of the neural substrates of executive functioning. *Human Brain Mapping*. 2005;25(4):409-423. doi:10.1002/hbm.20118

86. Saylik R, Williams AL, Murphy RA, Szameitat AJ. Characterising the unity and diversity of executive functions in a within-subject fMRI study. *Sci Rep*. 2022;12(1):8182. doi:10.1038/s41598-022-11433-z

87. Uddin LQ. Salience processing and insular cortical function and dysfunction. *Nat Rev Neurosci*. 2015;16(1):55-61. doi:10.1038/nrn3857

88. Rottschy C, Langner R, Dogan I, et al. Modelling neural correlates of working memory: A coordinate-based meta-analysis. *NeuroImage*. 2012;60(1):830-846. doi:10.1016/j.neuroimage.2011.11.050

89. Kim C, Johnson NF, Cilles SE, Gold BT. Common and Distinct Mechanisms of Cognitive Flexibility in Prefrontal Cortex. *Journal of Neuroscience*. 2011;31(13):4771-4779. doi:10.1523/JNEUROSCI.5923-10.2011

90. Kim C, Cilles SE, Johnson NF, Gold BT. Domain general and domain preferential brain regions associated with different types of task switching: A Meta-Analysis. *Human Brain Mapping*. 2012;33(1):130-142. doi:10.1002/hbm.21199

91. Brass M, Derrfuss J, Forstmann B, Cramon D. The role of the inferior frontal junction area in cognitive control. *Trends in Cognitive Sciences*. 2005;9(7):314-316. doi:10.1016/j.tics.2005.05.001

92. Obeso I, Robles N, Marrón EM, Redolar-Ripoll D. Dissociating the Role of the pre-SMA in Response Inhibition and Switching: A Combined Online and Offline TMS Approach. *Front Hum Neurosci*. 2013;7:150. doi:10.3389/fnhum.2013.00150

93. Chambers CD, Garavan H, Bellgrove MA. Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neuroscience & Biobehavioral Reviews*. 2009;33(5):631-646. doi:10.1016/j.neubiorev.2008.08.016

94. Wessel JR, Aron AR. On the Globality of Motor Suppression: Unexpected Events and Their Influence on Behavior and Cognition. *Neuron*. 2017;93(2):259-280. doi:10.1016/j.neuron.2016.12.013

95. Chang EF, Raygor KP, Berger MS. Contemporary model of language organization: an overview for neurosurgeons. *JNS*. 2015;122(2):250-261. doi:10.3171/2014.10.JNS132647

96. Voets NL, Bartsch A, Plaha P. Brain white matter fibre tracts: a review of functional neuro-oncological relevance. *Journal of Neurology, Neurosurgery & Psychiatry*. 2017;88(12):1017-1025. doi:10.1136/jnnp-2017-316170

97. Kinoshita M, Miyashita K, Tsutsui T, Furuta T, Nakada M. Critical Neural Networks in Awake Surgery for Gliomas. *Neurol Med Chir(Tokyo)*. 2016;56(11):674-686.

doi:10.2176/nmc.ra.2016-0069

98. Veldsman M, Tai XY, Nichols T, et al. Cerebrovascular risk factors impact frontoparietal network integrity and executive function in healthy ageing. *Nat Commun*. 2020;11(1):4340. doi:10.1038/s41467-020-18201-5

99. Jiang J, Bruss J, Lee WT, Tranel D, Boes AD. White matter disconnection of left multiple demand network is associated with post-lesion deficits in cognitive control. *Nat Commun*. 2023;14(1):1740. doi:10.1038/s41467-023-37330-1

100. Forkel SJ, Friedrich P, Thiebaut de Schotten M, Howells H. White matter variability, cognition, and disorders: a systematic review. *Brain Struct Funct*. 2022;227(2):529-544. doi:10.1007/s00429-021-02382-w

101. Duffau H. Stimulation mapping of white matter tracts to study brain functional connectivity. *Nat Rev Neurol*. 2015;11(5):255-265. doi:10.1038/nrneurol.2015.51

102. Duffau H, Capelle L, Sichez N, et al. Intraoperative mapping of the subcortical language pathways using direct stimulations. *Brain*. 2002;125(1):199-214. doi:10.1093/brain/awf016

103. Tate MC, Herbet G, Moritz-Gasser S, Tate JE, Duffau H. Probabilistic map of critical functional regions of the human cerebral cortex: Broca's area revisited. *Brain*. 2014;137(10):2773-2782. doi:10.1093/brain/awu168

104. Borchers S, Himmelbach M, Logothetis N, Karnath HO. Direct electrical stimulation of human cortex — the gold standard for mapping brain functions? *Nat Rev Neurosci*. 2012;13(1):63-70. doi:10.1038/nrn3140

105. Mandonnet E, Winkler PA, Duffau H. Direct electrical stimulation as an input gate into brain functional networks: principles, advantages and limitations. *Acta Neurochir*. 2010;152(2):185-193. doi:10.1007/s00701-009-0469-0

106. Bates E, Wilson SM, Saygin AP, et al. Voxel-based lesion–symptom mapping. *Nat Neurosci*. 2003;6(5):448-450. doi:10.1038/nn1050

107. Rorden C, Karnath HO. Using human brain lesions to infer function: a relic from a past era in the fMRI age? *Nat Rev Neurosci*. 2004;5(10):812-819. doi:10.1038/nrn1521

108. Vaidya AR, Pujara MS, Petrides M, Murray EA, Fellows LK. Lesion Studies in Contemporary Neuroscience. *Trends Cogn Sci*. 2019;23(8):653-671. doi:10.1016/j.tics.2019.05.009

109. Griffis JC, Metcalf NV, Corbetta M, Shulman GL. Structural Disconnections Explain Brain Network Dysfunction after Stroke. *Cell Reports*. 2019;28(10):2527-2540.e9. doi:10.1016/j.celrep.2019.07.100

110. Herbet G, Duffau H. Contribution of the medial eye field network to the voluntary deployment of visuospatial attention. *Nat Commun*. 2022;13(1):328. doi:10.1038/s41467-022-28030-3

111. Mah YH, Husain M, Rees G, Nachev P. Human brain lesion-deficit inference remapped. *Brain*. 2014;137(9):2522-2531. doi:10.1093/brain/awu164

112. Mah YH, Husain M, Rees G, Nachev P. The complexities of lesion-deficit inference in the human brain: Reply to Herbet et al. *Cortex*. 2015;64:417-419. doi:10.1016/j.cortex.2014.12.002

113. Schotten MT, Tomaiuolo F, Aiello M, et al. Damage to White Matter Pathways in Subacute and Chronic Spatial Neglect: A Group Study and 2 Single-Case Studies with Complete Virtual "In Vivo" Tractography Dissection. *Cerebral Cortex*. 2014;24(3):691-706. doi:10.1093/cercor/bhs351

114. Tournier JD, Mori S, Leemans A. Diffusion tensor imaging and beyond: Diffusion Tensor Imaging and Beyond. *Magn Reson Med*. 2011;65(6):1532-1556. doi:10.1002/mrm.22924

115. Oishi K, ed. *MRI Atlas of Human White Matter*. 2. ed. Elsevier, Acad. Press; 2011.

116. Roberts RE, Anderson EJ, Husain M. White Matter Microstructure and Cognitive Function. *The Neuroscientist*. 2013;19(1):8-15. doi:10.1177/1073858411421218

117. Dell'Acqua F, Simmons A, Williams SCR, Catani M. Can spherical deconvolution provide more information than fiber orientations? Hindrance modulated orientational anisotropy, a true-tract specific index to characterize white matter diffusion. *Human Brain Mapping*. 2013;34(10):2464-2483. doi:10.1002/hbm.22080

118. Winston GP. The physical and biological basis of quantitative parameters derived from

diffusion MRI. *Quant Imaging Med Surg*. 2012;2(4):254-265. doi:10.3978/j.issn.2223-4292.2012.12.05

119. Jensen JH, Helpern JA. MRI quantification of non-Gaussian water diffusion by kurtosis analysis. *NMR Biomed*. 2010;23(7):698-710. doi:10.1002/nbm.1518

120. Tabesh A, Jensen JH, Ardekani BA, Helpern JA. Estimation of tensors and tensor-derived measures in diffusional kurtosis imaging: Tensors and Tensor-Derived Measures in DKI. *Magn Reson Med*. 2011;65(3):823-836. doi:10.1002/mrm.22655

121. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. Published online March 29, 2021:n71. doi:10.1136/bmj.n71

122. Vienne A, Barrois RP, Buffat S, Ricard D, Vidal PP. Inertial Sensors to Assess Gait Quality in Patients with Neurological Disorders: A Systematic Review of Technical and Analytical Challenges. *Front Psychol*. 2017;8:817. doi:10.3389/fpsyg.2017.00817

123. Catani M, Howard RJ, Pajevic S, Jones DK. Virtual in Vivo Interactive Dissection of White Matter Fasciculi in the Human Brain. *NeuroImage*. 2002;17(1):77-94. doi:10.1006/nimg.2002.1136

124. Kinoshita M, Nakajima R, Shinohara H, et al. Chronic spatial working memory deficit associated with the superior longitudinal fasciculus: a study using voxel-based lesion-symptom mapping and intraoperative direct stimulation in right prefrontal glioma surgery. *JNS*. 2016;125(4):1024-1032. doi:10.3171/2015.10.JNS1591

125. Schotten MT, Urbanski M, Duffau H, et al. Direct Evidence for a Parietal-Frontal Pathway Subserving Spatial Awareness in Humans. *Science*. 2005;309(5744):2226-2228. doi:10.1126/science.1116251

126. Bartolomeo P, Thiebaut de Schotten M, Chica AB. Brain networks of visuospatial attention and their disruption in visual neglect. *Front Hum Neurosci*. 2012;6. doi:10.3389/fnhum.2012.00110

127. Nakajima R, Kinoshita M, Miyashita K, et al. Damage of the right dorsal superior longitudinal fascicle by awake surgery for glioma causes persistent visuospatial dysfunction. *Sci Rep*. 2017;7:17158. doi:10.1038/s41598-017-17461-4

128. Schotten MT, Dell'Acqua F, Forkel SJ, et al. A lateralized brain network for visuospatial attention. *Nature Neuroscience*. 2011;14(10):1245-1246. doi:10.1038/nn.2905

129. Papagno C, Comi A, Riva M, et al. Mapping the brain network of the phonological loop: The Phonological Loop Brain Network. *Hum Brain Mapp*. 2017;38(6):3011-3024. doi:10.1002/hbm.23569

130. Barbey AK, Koenigs M, Grafman J. Dorsolateral prefrontal contributions to human working memory. *Cortex*. 2013;49(5):1195-1205. doi:10.1016/j.cortex.2012.05.022

131. Catani M, Dell'Acqua F, Vergani F, et al. Short frontal lobe connections of the human brain. *Cortex*. 2012;48(2):273-291. doi:10.1016/j.cortex.2011.12.001

132. Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA. Triangulating a Cognitive Control Network Using Diffusion-Weighted Magnetic Resonance Imaging (MRI) and Functional MRI. *Journal of Neuroscience*. 2007;27(14):3743-3752. doi:10.1523/JNEUROSCI.0519-07.2007

133. Catani M, Mesulam MM, Jakobsen E, et al. A novel frontal pathway underlies verbal fluency in primary progressive aphasia. *Brain*. 2013;136(8):2619-2628. doi:10.1093/brain/awt163

134. Dick AS, Garic D, Graziano P, Tremblay P. The frontal aslant tract (FAT) and its role in speech, language and executive function. *Cortex*. 2019;111:148-163. doi:10.1016/j.cortex.2018.10.015

135. Kinoshita M, de Champfleur NM, Deverdun J, Moritz-Gasser S, Herbet G, Duffau H. Role of fronto-striatal tract and frontal aslant tract in movement and speech: an axonal mapping study. *Brain Struct Funct*. 2014;220(6):3399-3412. doi:10.1007/s00429-014-0863-0

136. Aron AR, Herz DM, Brown P, Forstmann BU, Zaghloul K. Frontosubthalamic Circuits for Control of Action and Cognition. *The Journal of Neuroscience*. 2016;36(45):11489-11495. doi:10.1523/JNEUROSCI.2348-16.2016

137. Rutten GJM, Landers MJF, De Baene W, Meijerink T, van der Hek S, Verheul JHB. Executive functional deficits during electrical stimulation of the right frontal aslant tract. *Brain Imaging and Behavior*. Published online January 19, 2021. doi:10.1007/s11682-020-00439-8

138. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp*. 2005;25(1):46-59. doi:10.1002/hbm.20131

139. Nakajima R, Okita H, Kinoshita M, et al. Direct evidence for the causal role of the left supplementary motor area in working memory: A preliminary study. *Clinical Neurology and Neurosurgery*. 2014;126:201-204. doi:10.1016/j.clineuro.2014.09.009

140. Cochereau J, Lemaitre AL, Wager M, Moritz-Gasser S, Duffau H, Herbet G. Network-behavior mapping of lasting executive impairments after low-grade glioma surgery. *Brain Struct Funct*. 2020;225(8):2415-2429. doi:10.1007/s00429-020-02131-5

141. Grahn JA, Parkinson JA, Owen AM. The cognitive functions of the caudate nucleus. *Progress in Neurobiology*. 2008;86(3):141-155. doi:10.1016/j.pneurobio.2008.09.004

142. Nakajima M, Halassa MM. Thalamic control of functional cortical connectivity. *Current Opinion in Neurobiology*. 2017;44:127-131. doi:10.1016/j.conb.2017.04.001

143. Kennedy KM, Raz N. Aging white matter and cognition: Differential effects of regional variations in diffusion properties on memory, executive functions, and speed. *Neuropsychologia*. 2009;47(3):916-927. doi:10.1016/j.neuropsychologia.2009.01.001

144. Zahr NM, Rohlfing T, Pfefferbaum A, Sullivan EV. Problem solving, working memory, and motor correlates of association and commissural fiber bundles in normal aging: a quantitative fiber tracking study. *Neuroimage*. 2009;44(3):1050-1062. doi:10.1016/j.neuroimage.2008.09.046

145. Charlton, Barrick, Lawes, Markus, Morris. White matter pathways associated with working memory in normal aging. *Cortex*. 2010;46(4):474-489. doi:10.1016/j.cortex.2009.07.005

146. Takeuchi H, Sekiguchi A, Taki Y, et al. Training of Working Memory Impacts Structural Connectivity. *Journal of Neuroscience*. 2010;30(9):3297-3303. doi:10.1523/JNEUROSCI.4611-09.2010

147. Charlton RA, Barrick TR, Markus HS, Morris RG. Verbal working and long-term episodic memory associations with white matter microstructure in normal aging investigated using tract-based spatial statistics. *Psychology and Aging*. 2013;28(3):768-777.

doi:10.1037/a0032668

148. Strenziok M, Greenwood PM, Santa Cruz SA, Thompson JC, Parasuraman R. Differential Contributions of Dorso-Ventral and Rostro-Caudal Prefrontal White Matter Tracts to Cognitive Control in Healthy Older Adults. Sirigu A, ed. *PLoS ONE*. 2013;8(12):e81410. doi:10.1371/journal.pone.0081410

149. Chung S, Fieremans E, Kucukboyaci NE, et al. Working Memory And Brain Tissue Microstructure: White Matter Tract Integrity Based On Multi-Shell Diffusion MRI. *Scientific Reports*. 2018;8(1). doi:10.1038/s41598-018-21428-4

150. Palacios EM, Fernandez-Espejo D, Junque C, et al. Diffusion tensor imaging differences relate to memory deficits in diffuse traumatic brain injury. *BMC Neurology*. 2011;11(1). doi:10.1186/1471-2377-11-24

151. Palacios EM, Sala-Llonch R, Junque C, et al. White matter integrity related to functional working memory networks in traumatic brain injury. *Neurology*. 2012;78(12):852-860. doi:10.1212/WNL.0b013e31824c465a

152. Li X, Salami A, Avelar-Pereira B, Bäckman L, Persson J. White-Matter Integrity and Working Memory: Links to Aging and Dopamine-Related Genes. *eNeuro*. 2022;9(2):ENEURO.0413-21.2022. doi:10.1523/ENEURO.0413-21.2022

153. Rizio AA, Diaz MT. Language, aging, and cognition: frontal aslant tract and superior longitudinal fasciculus contribute toward working memory performance in older adults. *NeuroReport*. 2016;27(9):689-693. doi:10.1097/WNR.0000000000000597

154. Burzynska AZ, Nagel IE, Preuschhof C, et al. Microstructure of Frontoparietal Connections Predicts Cortical Responsivity and Working Memory Performance. *Cerebral Cortex*. 2011;21(10):2261-2271. doi:10.1093/cercor/bhq293

155. Gallen CL, Turner GR, Adnan A, D'Esposito M. Reconfiguration of brain network architecture to support executive control in aging. *Neurobiology of Aging*. 2016;44:42-52. doi:10.1016/j.neurobiolaging.2016.04.003

156. Metzler-Baddeley C, Foley S, de Santis S, et al. Dynamics of White Matter Plasticity Underlying Working Memory Training: Multimodal Evidence from Diffusion MRI and Relaxometry. *Journal of Cognitive Neuroscience*. 2017;29(9):1509-1520.

doi:10.1162/jocn_a_01127

157. Dziemian S, Appenzeller S, von Bastian CC, Jäncke L, Langer N. Working Memory Training Effects on White Matter Integrity in Young and Older Adults. *Front Hum Neurosci*. 2021;15:605213. doi:10.3389/fnhum.2021.605213

158. Chung S, Wang X, Fieremans E, et al. Altered Relationship between Working Memory and Brain Microstructure after Mild Traumatic Brain Injury. *American Journal of Neuroradiology*. Published online August 1, 2019. doi:10.3174/ajnr.A6146

159. Yoon S, Kim J, Musen G, et al. Prefronto-temporal white matter microstructural alterations 20 years after the diagnosis of type 1 diabetes mellitus. *Pediatric Diabetes*. 2018;19(3):478-485. doi:10.1111/pedi.12574

160. Catani M, Thiebaut de Schotten M. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*. 2008;44(8):1105-1132. doi:10.1016/j.cortex.2008.05.004

161. Bubb EJ, Metzler-Baddeley C, Aggleton JP. The cingulum bundle: Anatomy, function, and dysfunction. *Neurosci Biobehav Rev*. 2018;92:104-127. doi:10.1016/j.neubiorev.2018.05.008

162. Bettcher BM, Mungas D, Patel N, et al. Neuroanatomical substrates of executive functions: Beyond prefrontal structures. *Neuropsychologia*. 2016;85:100-109. doi:10.1016/j.neuropsychologia.2016.03.001

163. Varriano F, Pascual-Diaz S, Prats-Galino A. When the FAT goes wide: Right extended Frontal Aslant Tract volume predicts performance on working memory tasks in healthy humans. He H, ed. *PLoS ONE*. 2018;13(8):e0200786. doi:10.1371/journal.pone.0200786

164. Varriano F, Pascual-Diaz S, Prats-Galino A. Distinct Components in the Right Extended Frontal Aslant Tract Mediate Language and Working Memory Performance: A Tractography-Informed VBM Study. *Front Neuroanat*. 2020;14:21. doi:10.3389/fnana.2020.00021

165. Salami A, Rieckmann A, Karalija N, et al. Neurocognitive Profiles of Older Adults with Working-Memory Dysfunction. *Cerebral Cortex*. Published online April 18, 2018. doi:10.1093/cercor/bhy062

166. Hegde RR, Kelly S, Lutz O, et al. Association of white matter microstructure and extracellular free-water with cognitive performance in the early course of schizophrenia. *Psychiatry Research: Neuroimaging*. 2020;305:111159. doi:10.1016/j.pscychresns.2020.111159

167. Muir RT, Lam B, Honjo K, et al. Trail Making Test Elucidates Neural Substrates of Specific Poststroke Executive Dysfunctions. *Stroke*. 2015;46(10):2755-2761. doi:10.1161/STROKEAHA.115.009936

168. Mandonnet E, Cerliani L, Siuda-Krzywicka K, et al. A network-level approach of cognitive flexibility impairment after surgery of a right temporo-parietal glioma. *Neurochirurgie*. 2017;63(4):308-313. doi:10.1016/j.neuchi.2017.03.003

169. Llinàs-Reglà J, Vilalta-Franch J, López-Pousa S, Calvó-Perxas L, Torrents Rodas D, Garre-Olmo J. The Trail Making Test: Association With Other Neuropsychological Measures and Normative Values for Adults Aged 55 Years and Older From a Spanish-Speaking Population-Based Sample. *Assessment*. 2017;24(2):183-196. doi:10.1177/1073191115602552

170. Sánchez-Cubillo I, Periáñez JA, Adrover-Roig D, et al. Construct validity of the Trail Making Test: Role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *J Int Neuropsychol Soc*. 2009;15(3):438-450. doi:10.1017/S1355617709090626

171. Kinnunen KM, Greenwood R, Powell JH, et al. White matter damage and cognitive impairment after traumatic brain injury. *Brain*. 2011;134(2):449-463. doi:10.1093/brain/awq347

172. Marchesi O, Bonacchi R, Valsasina P, et al. Functional and structural MRI correlates of executive functions in multiple sclerosis. *Mult Scler*. 2022;28(5):742-756. doi:10.1177/13524585211033184

173. Madden DJ, Bennett IJ, Song AW. Cerebral White Matter Integrity and Cognitive Aging: Contributions from Diffusion Tensor Imaging. *Neuropsychol Rev*. 2009;19(4):415. doi:10.1007/s11065-009-9113-2

174. Smolker HR, Friedman NP, Hewitt JK, Banich MT. Neuroanatomical Correlates of the

Unity and Diversity Model of Executive Function in Young Adults. *Front Hum Neurosci*. 2018;12:283. doi:10.3389/fnhum.2018.00283

175. Gold BT, Powell DK, Xuan L, Jicha GA, Smith CD. Age-related slowing of task switching is associated with decreased integrity of frontoparietal white matter. *Neurobiology of Aging*. 2010;31(3):512-522. doi:10.1016/j.neurobiolaging.2008.04.005

176. Jolly TAD, Cooper PS, Rennie JL, et al. Age-related decline in task switching is linked to both global and tract-specific changes in white matter microstructure: White Matter Effects on Task Switching. *Human Brain Mapping*. 2017;38(3):1588-1603. doi:10.1002/hbm.23473

177. Perry ME, McDonald CR, Hagler DJ, et al. White matter tracts associated with set-shifting in healthy aging. *Neuropsychologia*. 2009;47(13):2835-2842. doi:10.1016/j.neuropsychologia.2009.06.008

178. Bendlin BB, Fitzgerald ME, Ries ML, et al. White Matter in Aging and Cognition: A Cross-Sectional Study of Microstructure in Adults Aged Eighteen to Eighty-Three. *Developmental Neuropsychology*. 2010;35(3):257-277. doi:10.1080/87565641003696775

179. Kantarci K, Senjem ML, Avula R, et al. Diffusion tensor imaging and cognitive function in older adults with no dementia. *Neurology*. 2011;77(1):26-34. doi:10.1212/WNL.0b013e31822313dc

180. Herbet G, Zemmoura I, Duffau H. Functional Anatomy of the Inferior Longitudinal Fasciculus: From Historical Reports to Current Hypotheses. *Frontiers in Neuroanatomy*. 2018;12. doi:10.3389/fnana.2018.00077

181. Leunissen I, Coxon JP, Caeyenberghs K, Michiels K, Sunaert S, Swinnen SP. Task switching in traumatic brain injury relates to cortico-subcortical integrity. *Human Brain Mapping*. 2014;35(5):2459-2469. doi:10.1002/hbm.22341

182. Serbruyns L, Leunissen I, van Ruitenbeek P, et al. Alterations in brain white matter contributing to age-related slowing of task switching performance: The role of radial diffusivity and magnetization transfer ratio. *Human Brain Mapping*. 2016;37(11):4084-4098. doi:10.1002/hbm.23297

183. Spitz G, Maller JJ, O'Sullivan R, Ponsford JL. White Matter Integrity Following Traumatic Brain Injury: The Association with Severity of Injury and Cognitive Functioning. *Brain*

Topography. 2013;26(4):648-660. doi:10.1007/s10548-013-0283-0

184. Jacobs HIL, Leritz EC, Williams VJ, et al. Association between white matter microstructure, executive functions, and processing speed in older adults: The impact of vascular health. *Human Brain Mapping*. 2013;34(1):77-95. doi:10.1002/hbm.21412

185. MacPherson SE, Cox SR, Dickie DA, et al. Processing speed and the relationship between Trail Making Test-B performance, cortical thinning and white matter microstructure in older adults. *Cortex*. 2017;95:92-103. doi:10.1016/j.cortex.2017.07.021

186. Madden DJ, Spaniol J, Costello MC, et al. Cerebral white matter integrity mediates adult age differences in cognitive performance. *J Cogn Neurosci*. 2009;21(2):289-302. doi:10.1162/jocn.2009.21047

187. Puglisi G, Sciortino T, Rossi M, et al. Preserving executive functions in nondominant frontal lobe glioma surgery: an intraoperative tool. *Journal of Neurosurgery*. 2019;131(2):474-480. doi:10.3171/2018.4.JNS18393

188. Puglisi G, Howells H, Sciortino T, et al. Frontal pathways in cognitive control: direct evidence from intraoperative stimulation and diffusion tractography. 2019;142(8):2451-2465. doi:10.1093/brain/awz197

189. Satoer D, Visch-Brink E, Smits M, et al. Long-term evaluation of cognition after glioma surgery in eloquent areas. *J Neurooncol*. 2014;116(1):153-160. doi:10.1007/s11060-013-1275-3

190. Wolf D, Zschutschke L, Scheurich A, et al. Age-related increases in stroop interference: Delineation of general slowing based on behavioral and white matter analyses: Stroop Interference Increases with Age. *Human Brain Mapping*. 2014;35(5):2448-2458. doi:10.1002/hbm.22340

191. Mamiya PC, Richards TL, Kuhl PK. Right Forceps Minor and Anterior Thalamic Radiation Predict Executive Function Skills in Young Bilingual Adults. *Frontiers in Psychology*. 2018;9. doi:10.3389/fpsyg.2018.00118

192. Vanes LD, Mouchlianitis E, Wood TC, Shergill SS. White matter changes in treatment refractory schizophrenia: Does cognitive control and myelination matter? *NeuroImage: Clinical*. 2018;18:186-191. doi:10.1016/j.nicl.2018.01.010

193. Ohoshi Y, Takahashi S, Yamada S, et al. Microstructural abnormalities in callosal fibers and their relationship with cognitive function in schizophrenia: A tract-specific analysis study. *Brain and Behavior*. 2019;9(8). doi:10.1002/brb3.1357

194. Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y. Structural correlates of cognitive domains in normal aging with diffusion tensor imaging. *Brain Structure and Function*. 2012;217(2):503-515. doi:10.1007/s00429-011-0344-7

195. Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y. White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. *Frontiers in Neuroscience*. 2013;7. doi:10.3389/fnins.2013.00032

196. Fjell AM, Sneve MH, Grydeland H, Storsve AB, Walhovd KB. The Disconnected Brain and Executive Function Decline in Aging. *Cereb Cortex*. Published online April 12, 2016:bhw082. doi:10.1093/cercor/bhw082

197. Yeh P, Guan Koay C, Wang B, et al. Compromised Neurocircuitry in Chronic Blast-Related Mild Traumatic Brain Injury. *Hum Brain Mapp*. 2017;38(1):352-369. doi:10.1002/hbm.23365

198. Kubicki M, Niznikiewicz M, Connor E, et al. Relationship Between White Matter Integrity, Attention, and Memory in Schizophrenia: A Diffusion Tensor Imaging Study. *Brain Imaging and Behavior*. 2009;3(2):191-201. doi:10.1007/s11682-009-9061-8

199. Schermuly I, Fellgiebel A, Wagner S, et al. Association between cingulum bundle structure and cognitive performance: An observational study in major depression. *Eur psychiatr*. 2010;25(6):355-360. doi:10.1016/j.eurpsy.2010.05.001

200. Metzler-Baddeley C, Jones DK, Steventon J, Westacott L, Aggleton JP, O'Sullivan MJ. Cingulum Microstructure Predicts Cognitive Control in Older Age and Mild Cognitive Impairment. *Journal of Neuroscience*. 2012;32(49):17612-17619. doi:10.1523/JNEUROSCI.3299-12.2012

201. Garcia-Egan PM, Preston-Campbell RN, Salminen LE, et al. Behavioral inhibition corresponds to white matter fiber bundle integrity in older adults. *Brain Imaging and Behavior*. 2019;13(6):1602-1611. doi:10.1007/s11682-019-00144-1

202. Oertel-Knöchel V, Reinke B, Alves G, et al. Frontal white matter alterations are associated

with executive cognitive function in euthymic bipolar patients. *Journal of Affective Disorders*. 2014;155:223-233. doi:10.1016/j.jad.2013.11.004

203. Genova HM, DeLuca J, Chiaravalloti N, Wylie G. The relationship between executive functioning, processing speed, and white matter integrity in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*. 2013;35(6):631-641. doi:10.1080/13803395.2013.806649

204. Mamah D, Conturo TE, Harms MP, et al. Anterior thalamic radiation integrity in schizophrenia: A diffusion-tensor imaging study. *Psychiatry Research: Neuroimaging*. 2010;183(2):144-150. doi:10.1016/j.pscychresns.2010.04.013

205. Wagner G, Koch K, Schachtzabel C, et al. Structural basis of the fronto-thalamic dysconnectivity in schizophrenia: A combined DCM-VBM study. *NeuroImage: Clinical*. 2013;3:95-105. doi:10.1016/j.nicl.2013.07.010

206. Giraldo-Chica M, Rogers BP, Damon SM, Landman BA, Woodward ND. Prefrontal-Thalamic Anatomical Connectivity and Executive Cognitive Function in Schizophrenia. *Biological Psychiatry*. 2018;83(6):509-517. doi:10.1016/j.biopsych.2017.09.022

207. Wagner G, De la Cruz F, Schachtzabel C, et al. Structural and functional dysconnectivity of the fronto-thalamic system in schizophrenia: A DCM-DTI study. *Cortex*. 2015;66:35-45. doi:10.1016/j.cortex.2015.02.004

208. Zhang J, Wang Y, Wang J, et al. White matter integrity disruptions associated with cognitive impairments in type 2 diabetic patients. *Diabetes*. 2014;63(11):3596-3605. doi:10.2337/db14-0342

209. Hikosaka O, Isoda M. Switching from automatic to controlled behavior: cortico-basal ganglia mechanisms. *Trends in Cognitive Sciences*. 2010;14(4):154-161. doi:10.1016/j.tics.2010.01.006

210. Fu Z, Wu DAJ, Ross I, et al. Single-Neuron Correlates of Error Monitoring and Post-Error Adjustments in Human Medial Frontal Cortex. *Neuron*. 2019;101(1):165-177.e5. doi:10.1016/j.neuron.2018.11.016

211. Landers MJF, Sitskoorn MM, Rutten GJM, Mandonnet E, De Baene W. A systematic review of the use of subcortical intraoperative electrical stimulation mapping for monitoring

of executive deficits and neglect: what is the evidence so far? *Acta Neurochir*. 2022;164(1):177-191. doi:10.1007/s00701-021-05012-w

212. Rofes A, Mandonnet E, Godden J, et al. Survey on current cognitive practices within the European Low-Grade Glioma Network: towards a European assessment protocol. *Acta Neurochir*. 2017;159(7):1167-1178. doi:10.1007/s00701-017-3192-2

213. Lemaitre AL, Herbet G, Ng S, Moritz-Gasser S, Duffau H. Cognitive preservation following awake mapping-based neurosurgery for low-grade gliomas: A longitudinal, within-patient design study. *Neuro Oncol*. 2022;24(5):781-793. doi:10.1093/neuonc/noab275

214. Schmitt LI, Wimmer RD, Nakajima M, Happ M, Mofakham S, Halassa MM. Thalamic amplification of cortical connectivity sustains attentional control. *Nature*. 2017;545(7653):219-223. doi:10.1038/nature22073

215. Inglese M, Makani S, Johnson G, et al. Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *Journal of Neurosurgery*. 2005;103(2):298-303. doi:10.3171/jns.2005.103.2.0298

216. Ljungqvist J, Nilsson D, Ljungberg M, et al. Longitudinal study of the diffusion tensor imaging properties of the corpus callosum in acute and chronic diffuse axonal injury. *Brain Injury*. 2011;25(4):370-378. doi:10.3109/02699052.2011.558038

217. Sidaros A, Engberg AW, Sidaros K, et al. Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. *Brain*. 2008;131(2):559-572. doi:10.1093/brain/awm294

218. Tzourio-Mazoyer N. Intra- and Inter-hemispheric Connectivity Supporting Hemispheric Specialization. In: Kennedy H, Van Essen DC, Christen Y, eds. *Micro-, Meso- and Macro-Connectomics of the Brain*. Springer International Publishing; 2016:129-146. doi:10.1007/978-3-319-27777-6_9

219. De Benedictis A, Petit L, Descoteaux M, et al. New insights in the homotopic and heterotopic connectivity of the frontal portion of the human corpus callosum revealed by microdissection and diffusion tractography: Homo- and Hetero-Topic Fronto-Callosal Connectivity. *Hum Brain Mapp*. 2016;37(12):4718-4735. doi:10.1002/hbm.23339

220. Freeze WM, Zanon Zotin MC, Scherlek AA, et al. Corpus callosum lesions are associated

with worse cognitive performance in cerebral amyloid angiopathy. *Brain Communications*. 2022;4(3):fcac105. doi:10.1093/braincomms/fcac105

221. Bodini B, Cercignani M, Khaleeli Z, et al. Corpus callosum damage predicts disability progression and cognitive dysfunction in primary-progressive MS after five years. *Hum Brain Mapp*. 2013;34(5):1163-1172. doi:10.1002/hbm.21499

222. Sui J, Qi S, van Erp TGM, et al. Multimodal neuromarkers in schizophrenia via cognition-guided MRI fusion. *Nat Commun*. 2018;9(1):3028. doi:10.1038/s41467-018-05432-w

223. Makris N, Kennedy DN, McInerney S, et al. Segmentation of Subcomponents within the Superior Longitudinal Fascicle in Humans: A Quantitative, In Vivo, DT-MRI Study. *Cerebral Cortex*. 2005;15(6):854-869. doi:10.1093/cercor/bhh186

224. Schmahmann JD, Pandya DN, Wang R, et al. Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. *Brain*. 2007;130(3):630-653. doi:10.1093/brain/awl359

225. Nakajima R, Kinoshita M, Shinohara H, Nakada M. The superior longitudinal fascicle: reconsidering the fronto-parietal neural network based on anatomy and function. *Brain Imaging and Behavior*. Published online August 29, 2019. doi:10.1007/s11682-019-00187-4

226. Parlatini V, Radua J, Dell'Acqua F, et al. Functional segregation and integration within fronto-parietal networks. *NeuroImage*. 2017;146:367-375. doi:10.1016/j.neuroimage.2016.08.031

227. Budisavljevic S, Dell'Acqua F, Zanatto D, et al. Asymmetry and Structure of the Fronto-Parietal Networks Underlie Visuomotor Processing in Humans. *Cereb Cortex*. Published online January 11, 2016:bhv348. doi:10.1093/cercor/bhv348

228. Maldonado IL, Moritz-Gasser S, de Champfleur NM, Bertram L, Moulinié G, Duffau H. Surgery for gliomas involving the left inferior parietal lobule: new insights into the functional anatomy provided by stimulation mapping in awake patients: Clinical article. *JNS*. 2011;115(4):770-779. doi:10.3171/2011.5.JNS112

229. Jones DK, Christiansen KF, Chapman RJ, Aggleton JP. Distinct subdivisions of the cingulum bundle revealed by diffusion MRI fibre tracking: Implications for neuropsychological investigations. *Neuropsychologia*. 2013;51(1):67-78.

doi:10.1016/j.neuropsychologia.2012.11.018

230. Wu Y, Sun D, Wang Y, Wang Y, Ou S. Segmentation of the Cingulum Bundle in the Human Brain: A New Perspective Based on DSI Tractography and Fiber Dissection Study. *Front Neuroanat.* 2016;10. doi:10.3389/fnana.2016.00084

231. Yeager BE, Bruss J, Duffau H, et al. Central precuneus lesions are associated with impaired executive function. *Brain Struct Funct.* 2022;227(9):3099-3108. doi:10.1007/s00429-022-02556-0

232. Vassal F, Boutet C, Lemaire JJ, Nuti C. New insights into the functional significance of the frontal aslant tract: An anatomo–functional study using intraoperative electrical stimulations combined with diffusion tensor imaging-based fiber tracking. *British Journal of Neurosurgery*. 2014;28(5):685-687. doi:10.3109/02688697.2014.889810

233. Zhong AJ, Baldo JV, Dronkers NF, Ivanova MV. The unique role of the frontal aslant tract in speech and language processing. *NeuroImage: Clinical*. 2022;34:103020. doi:10.1016/j.nicl.2022.103020

234. Li M, Zhang Y, Song L, et al. Structural connectivity subserving verbal fluency revealed by lesion-behavior mapping in stroke patients. *Neuropsychologia*. 2017;101:85-96. doi:10.1016/j.neuropsychologia.2017.05.008

235. Neef NE, Anwander A, Bütfering C, et al. Structural connectivity of right frontal hyperactive areas scales with stuttering severity. *Brain*. 2018;141(1):191-204. doi:10.1093/brain/awx316

236. Nachev P, Wydell H, O’neill K, Husain M, Kennard C. The role of the pre-supplementary motor area in the control of action. *Neuroimage*. 2007;36 Suppl 2(3-3):T155-163. doi:10.1016/j.neuroimage.2007.03.034

237. Nachev P, Kennard C, Husain M. Functional role of the supplementary and pre-supplementary motor areas. *Nat Rev Neurosci*. 2008;9(11):856-869. doi:10.1038/nrn2478

238. Erika-Florence M, Leech R, Hampshire A. A functional network perspective on response inhibition and attentional control. *Nat Commun*. 2014;5(1):4073. doi:10.1038/ncomms5073

239. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: one decade on. *Trends in Cognitive Sciences*. 2014;18(4):177-185. doi:10.1016/j.tics.2013.12.003

240. Nakajima R, Kinoshita M, Nakada M. Simultaneous Damage of the Cingulate Cortex Zone II and Fronto-Striatal Circuit Causes Prolonged Selective Attentional Deficits. *Front Hum Neurosci*. 2021;15:762578. doi:10.3389/fnhum.2021.762578

241. Biesbroek JM, Kuijf HJ, van der Graaf Y, et al. Association between Subcortical Vascular Lesion Location and Cognition: A Voxel-Based and Tract-Based Lesion-Symptom Mapping Study. The SMART-MR Study. Scuteri A, ed. *PLoS ONE*. 2013;8(4):e60541. doi:10.1371/journal.pone.0060541

242. Zhang R, Beyer F, Lampe L, et al. White matter microstructural variability mediates the relation between obesity and cognition in healthy adults. *NeuroImage*. 2018;172:239-249. doi:10.1016/j.neuroimage.2018.01.028

243. Halassa MM, Kastner S. Thalamic functions in distributed cognitive control. *Nat Neurosci*. 2017;20(12):1669-1679. doi:10.1038/s41593-017-0020-1

244. Braun U, Schäfer A, Walter H, et al. Dynamic reconfiguration of frontal brain networks during executive cognition in humans. *Proceedings of the National Academy of Sciences*. 2015;112(37):11678-11683. doi:10.1073/pnas.1422487112

245. Nomura K, Kazui H, Tokunaga H, et al. Possible Roles of the Dominant Uncinate Fasciculus in Naming Objects: A Case Report of Intraoperative Electrical Stimulation on a Patient with a Brain Tumour. *Behavioural Neurology*. 2013;27(2):229-234. doi:10.1155/2013/267408

246. Baddeley AD. *Working Memory, Thought, and Action*. Oxford University Press; 2007.

247. Herbet G, Yordanova YN, Duffau H. Left Spatial Neglect Evoked by Electrostimulation of the Right Inferior Fronto-occipital Fasciculus. *Brain Topography*. 2017;30(6):747-756. doi:10.1007/s10548-017-0574-y

248. Urbanski M, Thiebaut de Schotten M, Rodrigo S, et al. Brain networks of spatial awareness: evidence from diffusion tensor imaging tractography. *Journal of Neurology, Neurosurgery & Psychiatry*. 2008;79(5):598-601. doi:10.1136/jnnp.2007.126276

249. Martino J, Brogna C, Robles SG, Vergani F, Duffau H. Anatomic dissection of the inferior fronto-occipital fasciculus revisited in the lights of brain stimulation data☆. *Cortex*. 2010;46(5):691-699. doi:10.1016/j.cortex.2009.07.015

250. Herbet G, Moritz-Gasser S, Duffau H. Direct evidence for the contributive role of the right inferior fronto-occipital fasciculus in non-verbal semantic cognition. *Brain Struct Funct*. 2017;222(4):1597-1610. doi:10.1007/s00429-016-1294-x

251. Voineskos AN, Rajji TK, Lobaugh NJ, et al. Age-related decline in white matter tract integrity and cognitive performance: A DTI tractography and structural equation modeling study. *Neurobiology of Aging*. 2012;33(1):21-34. doi:10.1016/j.neurobiolaging.2010.02.009

252. Welsh MC, Satterlee-Cartmell T, Stine M. Towers of Hanoi and London: Contribution of working memory and inhibition to performance. *Brain and cognition*. 1999;41(2):231-242.

253. Cocchi L, Zalesky A, Fornito A, Mattingley JB. Dynamic cooperation and competition between brain systems during cognitive control. *Trends in Cognitive Sciences*. 2013;17(10):493-501. doi:10.1016/j.tics.2013.08.006

254. Finc K, Bonna K, He X, et al. Dynamic reconfiguration of functional brain networks during working memory training. *Nat Commun*. 2020;11(1):2435. doi:10.1038/s41467-020-15631-z

255. Duffau H. The huge plastic potential of adult brain and the role of connectomics: New insights provided by serial mappings in glioma surgery. *Cortex*. 2014;58:325-337. doi:10.1016/j.cortex.2013.08.005

256. Duffau H, Mandonnet E. The “onco-functional balance” in surgery for diffuse low-grade glioma: integrating the extent of resection with quality of life. *Acta Neurochir (Wien)*. 2013;155(6):951-957. doi:10.1007/s00701-013-1653-9

257. Mandonnet E, Herbet G, Duffau H. Letter: Introducing New Tasks for Intraoperative Mapping in Awake Glioma Surgery: Clearing the Line Between Patient Care and Scientific Research. *Neurosurgery*. 2020;86(2):E256-E257. doi:10.1093/neuros/nyz447

258. Makale MT, McDonald CR, Hattangadi-Gluth JA, Kesari S. Mechanisms of radiotherapy-

associated cognitive disability in patients with brain tumours. *Nature Reviews Neurology*. 2017;13(1):52-64. doi:10.1038/nrneurol.2016.185

259. Chapman CH, Zhu T, Nazem-Zadeh M, et al. Diffusion tensor imaging predicts cognitive function change following partial brain radiotherapy for low-grade and benign tumors. *Radiotherapy and Oncology*. 2016;120(2):234-240. doi:10.1016/j.radonc.2016.06.021

260. Zhu T, Chapman CH, Tsien C, et al. Effect of the Maximum Dose on White Matter Fiber Bundles Using Longitudinal Diffusion Tensor Imaging. *International Journal of Radiation Oncology*Biology*Physics*. 2016;96(3):696-705. doi:10.1016/j.ijrobp.2016.07.010

261. Connor M, Karunamuni R, McDonald C, et al. Regional susceptibility to dose-dependent white matter damage after brain radiotherapy. *Radiotherapy and Oncology*. 2017;123(2):209-217. doi:10.1016/j.radonc.2017.04.006

262. Gondi V, Pugh SL, Tome WA, et al. Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial. *Journal of Clinical Oncology*. 2014;32(34):3810-3816. doi:10.1200/JCO.2014.57.2909

Figure legends

Figure 1 Selection of studies of correlations of white matter tracts with executive functions.

Figure 2 Evidence of white matter tracts involvement in executive functions. Causal and correlation evidence are represented for each executive process and white matter tracts. The colors of the circles represent the total number of participants included in each study; the width of the circles represent the number of included studies that reported significant associations (Supplementary Table 1). The white matter tracts were generated from the Human Connectome Project tractography atlas: https://sites.google.com/a/labsolver.org/brain/diffusion-mri-templates/tractography (Yeh FC. *Population-Based Tract-To-Region Connectome of the Human Brain and Its Hierarchical Topology*. In Review; 2021. doi:10.21203/rs.3.rs-1083262/v1). CC, corpus callosum; AF, arcuate fasciculus; SLF, superior longitudinal fasciculus; Cing, cingulum bundle; FAT, frontal aslant tract; CST, cortico striatal tract; TR, thalamic radiation.

Box 1 Executive functions: conceptual framework and assessment

Executive functions, or cognitive control functions, are high-level cognitive processes serving goal-directed behaviors and flexible adjustment to the environment, as opposed to habits and automatic information processing. They also underpin behavioral processes such as initiation and emotional control, enabling individuals to regulate their thoughts and actions.[37–39] The broad concept of executive functions encompasses a wide set of cognitive abilities such as attentional control,[40–42] that is critical for monitoring, maintaining task goals and selecting relevant information in conditions of interference[43]; working memory, cognitive flexibility, inhibitory control.[40,44] These processes engage simultaneously during complex mental functions such as abstraction, planning, reasoning and decision-making, in a context-sensitive manner.[44]

The neuropsychological assessment of executive functions involve complex and multifactorial tasks that tap executive and low-level non-executive processes.[44] According to an influential conceptual framework that used latent variable analysis, some of the most frequent tests share a common variance reflecting a common underlying executive ability (the unity of executive functions, termed Common EF), but are still separable in three core executive processes: updating (working memory), shifting between tasks or mental sets, and inhibition of prepotent responses.[44] The development of the unity/diversity model, further exploring the interrelations and specificities of the three core executive processes, corroborates the specificity of working memory/updating and shifting abilities. However, an inhibition-specific factor could not be extracted after accounting for the Common EF factor, despite the fact that all the tasks employed to assess the three executive constructs load on the Common EF factor.[45] According to the authors, the Common EF reflects the ability to maintain, manage and leverage goals to influence ongoing processes, a general requirement of all executive tasks that may be central for response inhibition.[40] This mechanism would explain the absence of an additional inhibition-specific factor and aligns with research suggesting that brain activations underlying top-down inhibition may be reflecting context-monitoring, top-down activation of correct responses. Thus, at the neural level inhibition would emerge as an outcome of the interplay between goal-maintenance and suppression of irrelevant responses.[46,47]

There are several conceptualizations and different levels of complexity to describe executive functions.[48–51] The unity/diversity framework[44] contributed to addressing the problem of task impurity, which helps to guide the choice of constructs and tasks used in research. The three core executive domains have been commonly explored[39] in studies investigating the neural correlates underlying this complex and multifaceted cognitive construct.[50]

Working memory

Working memory relates to the ability to transiently process, maintain and use information input from diverse sensorial stimuli to serve ongoing tasks and future goal-directed behavior. The working memory system is characterized by limited capacity and implies an interaction among different levels of cognitive processing, sensorimotor mechanisms and activation of long-term memory representations.[52,53] Baddeley's theory conceptualizes a multicomponent model of working memory, a system with distinct but interconnected components allowing for temporary storage and manipulation of visuospatial (visuospatial sketchpad) and verbal information (phonological loop) and a system performing attentional control of action (central executive). The central executive would manage attentional resources, deploying them between visual and verbal stimuli modalities, updating representations and task shifting. A subsystem of the central executive, the episodic buffer, holds multimodal representations and links working memory to perception and long-term memory[52,54,55]

Working memory and updating abilities are assessed with tasks such as digit-spans backwards, Wechsler Adult Intelligence Scale's letter-number sequencing[56] and n-back tasks.[57]

Shifting

Our constantly changing environment requires flexible reorientation of our attention from one stimulus or mental representation to another, to adapt our behavior to the demands of new situations or to solve new problems based on acquired experience. Flexibility is a main component of executive functions and relates to the ability of shifting between tasks or mental sets.[58,59] It encompasses several cognitive processes such as detecting salient stimuli and focusing on it, retaining relevant information and rules representations, and inhibiting previous responses according to the appropriate strategy.[60] In other words, the successful completion of tests assessing task or set shifting abilities requires interactions among attentional processes, working memory and to a greater extent, inhibition of salient but unsuitable responses.[58]

The Trail-Making Test B (TMT-B)[61] and the Wisconsin Card Sorting Test[62] are some of the tasks frequently used for assessing set-shifting abilities in both clinical and research settings. For research purposes, different paradigms allowing the estimation of switch costs between tasks conditions have been developed to assess cognitive flexibility.[59]

Inhibition

Inhibition is a multifaceted concept[63] with multiple taxonomies[64] that encompasses behavioral (inhibition of impulses, unwanted memories and contextually inappropriate behaviors)[39,65–67] and cognitive processes (i.e., inhibition of automatic, prepotent responses).[44,64] It relates to the ability to deliberately suppress dominant, automatic responses and resist interference from environmental cues[39] to focus on information that is relevant to the accomplishment of ongoing tasks.

The completion of tasks assessing response inhibition involve other cognitive mechanisms such as working memory, resistance to proactive and retroactive interference,[64] and especially attentional control.[39] Inhibitory control of attention (interference control at the level of perception) enables stimuli selection and suppression of involuntary attention driven by the properties of stimuli themselves.[39,43] Such selective control of attention is essential for the maintenance and manipulation of information in working memory[39] and flexible responses,[58,64] fostering goal-directed behavior.

Several tasks and paradigms allow for testing inhibition and inhibition-related abilities.[64,68] In clinical practice, the assessment focus on the ability of deliberately suppress dominant, automatic responses and resist interference from environmental cues,[64] using tasks such as the Stroop task,[69] Tower of Hanoi and Tower of London,[44,70]and Go-No Go tasks.[71]

Box 2 Techniques for the identification of white matter tracts and assessment of white matter damage

Causal evidence: direct electrical stimulation and voxel-based lesion symptom mapping studies

Intraoperative brain mapping and lesion studies provide causal evidence of relationships between brain structure and function. Intraoperative brain mapping, performed during awake surgery using DES, has greatly contributed to understanding brain processing, especially the role of white matter tracts in cognition and behavior.[101] Generally used during resection of brain tumors such as gliomas, DES to exposed cortical and subcortical brain regions while the patient is performing different cognitive tasks allows for identifying brain areas whose stimulation induces transitory disruption of performance, providing real-time anatomo-functional correlations.[31] Along with lesion-induced reorganization of functional areas (brain plasticity), intraoperative brain mapping allows for maximal tumor resection while sparing cognitive functions even for lesions located near or within highly eloquent regions.[102] Beyond its undeniable surgical interest, DES remains the only technique that allows for direct in-vivo mapping of human white matter tracts.[31,101,103] However, the physiology of DES at the cellular and cortical levels is not completely understood,[101,104] and some limitations regarding the types of responses elicited by the stimulation must be considered. For example, DES may induce different behavioral responses at the same cortical region, or false negatives, which may occur particularly when the task is not rigorously chosen.[104,105] These limits are intrinsic to the complexity of the brain's functioning and network architecture because complex responses are rarely supported by one single brain region.[31] Perhaps one of the most challenging aspects of intraoperative brain mapping is that complex cognitive tasks routinely administered in standard neuropsychological assessments are not feasible during awake surgery, which may limit the mapping of higher-order cognitive processes.[101] Accurate results depend on the most rigorous control of the technical setting (i.e., appropriate tasks, intensity, and duration of stimulation, neuroimaging protocols) and the closest observation of the patient's overall state, notably their fatigue, which will indeed guide the entire procedure.[104,105]

Lesion mapping provides a powerful tool for identifying brain regions that are critical for a given cognitive task. In lesion studies using voxel-based lesion-symptom mapping, inferences are based on statistical analyses of the relation between tissue damage and brain function on a voxel-by-voxel basis, taking into account individual variability of spatial location of lesions, thus without constraints related to spatial resolution.[106] However, several aspects need to be considered to avoid biased interpretations. Deficits may occur not only because a given brain region is damaged but also from disconnection mechanisms, which implies that structurally healthy regions may have their function impaired. Moreover, brain plasticity may induce functional reorganization of brain regions in response to damage.[107] For the analysis of white matter tracts, the output statistical map, which reflects the degree of statistical association between lesioned voxels and behavioral performance, is typically overlaid by a white matter atlas, which allows for making inferences on the contribution of tracts to a given symptom/function.[108] Results must be interpreted with caution because voxel-based symptom mapping approaches are ill conceived to provide biologically plausible anatomo-functional correlations with white matter pathways. Other neuropsychological evidence is derived from tract-based lesion-symptom analyses or disconnection-symptom mapping that more directly correlate measures of disconnection severity to behavioral performance, at the level of the tract (e.g. lesion load, probability of disconnection) or the level of the voxel (e.g., whole-brain disconnection maps).[108–113]

Correlation evidence: neuroimaging techniques

MRI techniques can provide rich and complementary information to probe white matter microstructural integrity. Diffusion-weighted sequences are particularly useful in providing quantitative measurements characterizing the diffusion properties of water molecules, which can be linked to alterations of the microstructure. Additionally, these sequences help to recover the geometry of the major white matter bundles using tractography algorithms.[114]

Diffusion-weighted acquisitions consist of several images characterizing the diffusion properties in several directions (i.e., diffusion gradient sampling scheme) and according to potentially various diffusion weighting (i.e., b-values). Diffusion tensor imaging (DTI) is one of the most used techniques, relying on the assumption that diffusion properties can be modeled by a six-parameters tensor (i.e., a symmetric 3x3 matrix), from which several DTI metrics can be derived. Fractional anisotropy (FA) is a measure ranging from 0 to 1 that quantifies diffusion anisotropy[115]; regions with high FA values correspond to more organized and aligned neural pathways. The mean diffusivity (MD) reflects the average magnitude of water diffusion regardless of direction. Pathological processes that disrupt the integrity of white matter tracts are often associated with increased MD and decreased FA.[116] Axial diffusivity (i.e., diffusivity of water molecules along the principal axis of white matter fibers) and radial diffusivity (i.e., diffusivity of water molecules perpendicular to the principal axis of white matter fibers) are complementary measures that help to more finely characterize the microstructural properties of brain tissue, especially for investigating the integrity of the myelin sheath or the axonal membrane.[114] DTI techniques present some limitations regarding the identification of "kissing" or "crossing" fibers.[117] More involved diffusion model can be considered such as multi-compartment model, which can be used to disentangle intra-cellular from extra-cellular diffusion properties, diffusion kurtosis imaging (DKI), which expands on the standard DTI model by incorporating information about non-Gaussian diffusion, or methods based on the estimation of orientation distribution function,[117–119] allowing for the reconstruction of multiple fiber orientations.[114] The use of such diffusion models requires diffusion weighted sequences with a high number of diffusion gradient directions, typically ranging from 30 to 100, and with several b-values, resulting in a quite long acquisition duration, which limits their use in research settings.[120]

Tractography algorithms are computational methods that aim at reconstructing the geometry of white matter tracts in the brain from diffusion weighted MRI acquisition. There are several tractography algorithms available, including deterministic and probabilistic methods. Deterministic methods, generate tractography by following the direction of maximum diffusion along the estimated fiber tract. These algorithms generate a single fiber trajectory for each seed point. Probabilistic tractography algorithms generate a probability distribution for the possible fiber pathways, rather than a single trajectory.[114]

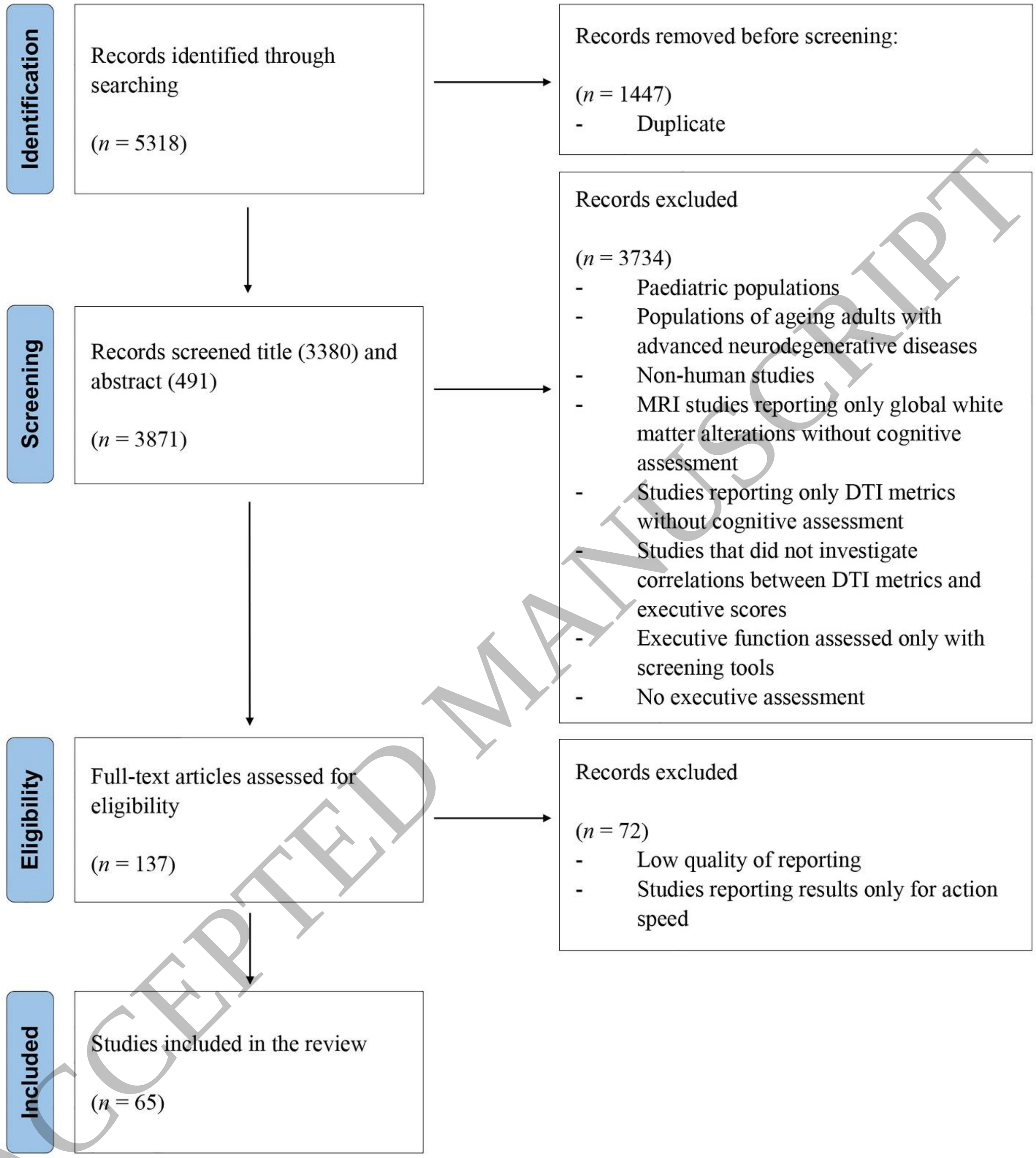

Figure 1

500x559 mm (x DPI)

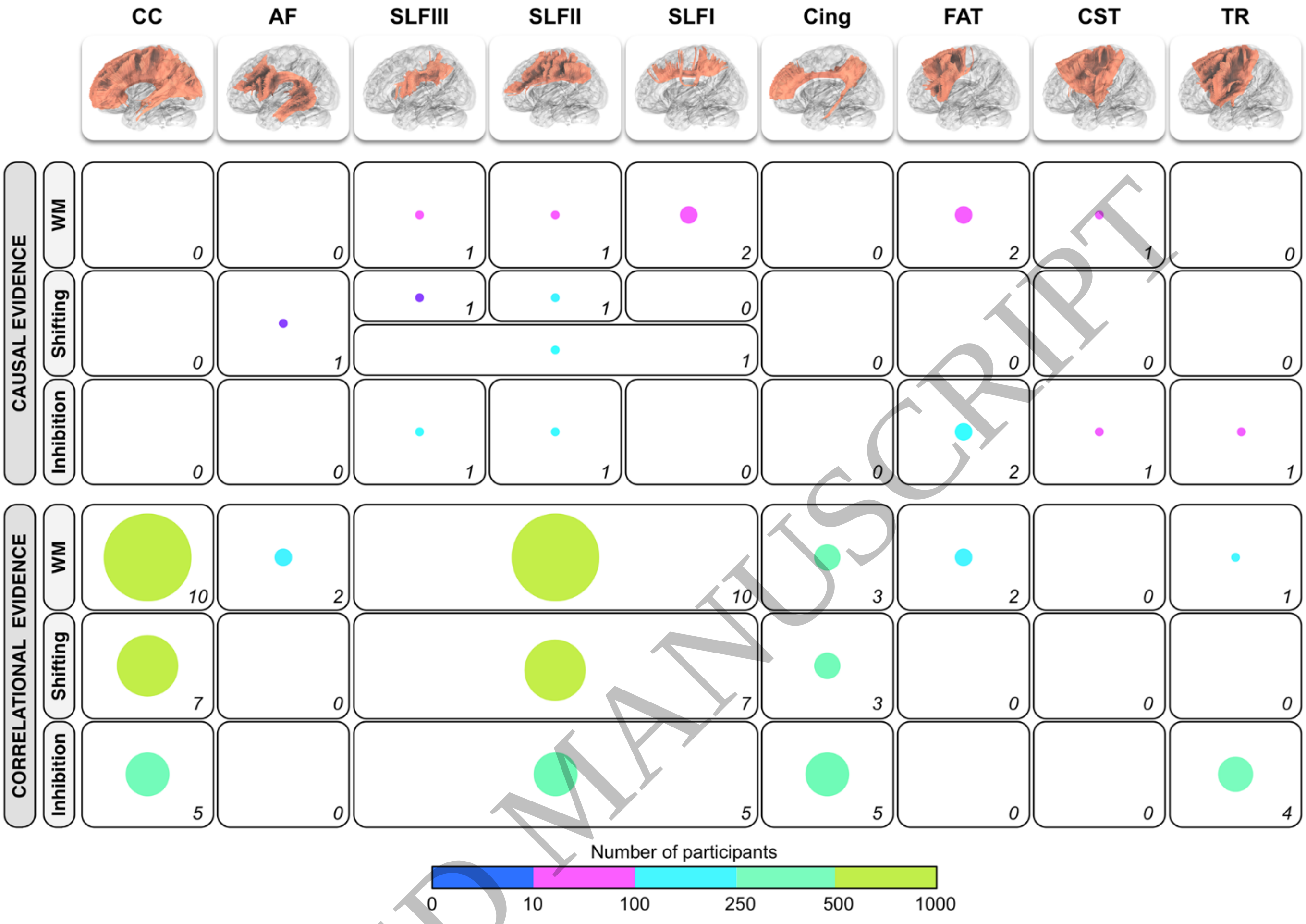

Figure 2

180x128 mm (x DPI)