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REVIEW ARTICLE

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White matter tracts and executive functions: a review of

causal and correlation evidence

4 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 © The Author(s) 2023. Published by Oxford University Press on behalf of the Guarantors of Brain. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com This article is published and distributed under the terms of the Oxford University Press, Standard Journals Publication Model 1 (https://academic.oup.com/pages/standard-publication-reuse-rights)

1 and clinical implications for individuals with brain tumors.

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- 19 **Running title:** White matter tracts and executive functions
- 20 **Keywords:** superior longitudinal fasciculus; cognitive control; diffusion tensor imaging; awake
- 21 surgery; voxel-based lesion-symptom mapping; tract-based lesion-symptom mapping
- 22 **Abbreviations:** AF = arcuate fasciculus; CC = corpus callosum; CR = corona radiata; DES =
- 23 direct electrical stimulation; D-FPN = dorsal fronto-parietal network; DKI = diffusion kurtosis
- imaging; DTI = diffusion tensor imaging; EC = external capsule; FA = fractional anisotropy;
- 25 FAT = frontal aslant tract; FPN = fronto-parietal network; IC = internal capsule; IFG = inferior
- 26 frontal gyrus; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus;
- 27 L-FPN = lateral fronto-parietal network; M-CIN = midcingulo-insular network; MD = mean

- 1 diffusivity; PFC = prefrontal cortex; SMA = supplementary motor area; SLF = superior
- 2 longitudinal fasciculus; pre-SMA = pre-supplementary motor areas; ROI = Region of Interest;
- 3 TMT-B = Trail Making Test B; TR = thalamic radiation

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Introduction

6 Complex and flexible cognitive processes are underpinned by widely distributed neural systems

7 in the human brain, $^{1-3}$ connected by white matter tracts that support structural connectivity, thus

8 enabling information transfer among brain areas and network integration. The central role of

9 white matter in human behavior and learning has been demonstrated in studies showing clear

10 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}

12 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, 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

22 underlying information processing and connect remote grey matter zones into communicating

23 neural assembles. In this vein, current neuroanatomical models explaining brain dysfunction

24 combine the roles of cortical brain zones and axonal connections in a "hodotopical"

25 approach.¹⁴According to this theoretical framework, brain dysfunction may result from

26 "topological" mechanisms (i.e., cortical lesions) or "hodological" mechanisms (i.e., lesions in

27 axonal pathways underlying connections among brain zones).

28 In light of these descriptions, disconnection mechanisms have been hypothesized to explain

29 cognitive dysfunction associated with brain pathologies affecting white matter such as traumatic

brain injury, 15-17 multiple sclerosis 18,19 and c erebrovascular disease, for example. 20 Also, 1 2 disconnection mechanisms and dysfunction of neural networks are thought be involved in the 3 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 4 normal aging processes²³: white matter microstructure damage and subsequent disconnection 5 mechanisms are a central hypothesis explaining the decline or change in cognitive functioning. 24-6 7 ²⁷Changes in brain architecture related to glioma growth and subsequent post-lesional neuroplasticity clearly revealed the key role of white matter, particularly regarding the dynamics 8 9 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-10 synaptic reorganization and recruitment of adjacent or even contralateral zones for functional 11 compensation of damaged areas, leading to significant changes in neural network architecture.³⁰ 12 These changes give opportunities for optimal tumor resection, because resection boundaries can 13 be defined according to individual perioperative responses triggered during direct electrical 14 stimulation (DES),³¹ as long as subcortical connectivity is identified and preserved.^{29,32} 15 Impairment of executive functions (Box 1) is indeed a common and perhaps a core deficit in 16 brain conditions with predominant white matter damage. 33-35 Such deficits may severely 17 compromise independence and quality of life because of their impact on professional, social, and 18

Neural networks supporting executive functions

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

emotional functioning.³⁶

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- According to a review article that introduced a new taxonomy for the large-scale functional
- 27 networks in the human brain, 77 three functional networks would be prominently involved in
- 28 executive functions: the dorsal fronto-parietal (D-FPN), lateral fronto-parietal (L-FPN) and
- 29 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. 80It 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

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. 88Task-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

1 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, 2 3 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 4 5 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 6 7 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 8 specific tracts can prominently support executive functions (i.e., tracts consistently associated 9 with executive functions across tasks, populations, and according to different levels of 10 evidence). 100 11 12 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, 13 lesion mapping and diffusion MRI techniques.(Box 2) We focused on the three constructs 14 defined in the unity/diversity of executive functions model, commonly assessed in in clinical 15

practice^{36,44}and research, 83,84 namely working memory/updating, set-shifting and inhibition of

Methods

prepotent responses. 40,44

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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

- 1 "awake surgery", "diffusion tensor imaging", "tract-based lesion-symptom mapping", "voxel-
- 2 based lesion-symptom mapping", "white matter". We selected studies and reviewed references of
- 3 included studies that could be relevant.(Fig.1) The procedures used in each study to avoid bias
- 4 and validate their methods were rated according to PRISMA guidelines, ¹²¹ using a checklist
- 5 adapted from previous work. 122 (Supplementary material) Briefly, we used the following basic
- 6 criteria to rate the studies: sufficient description of population sources and report of confounders,
- 7 sufficient detail of the protocol for reproducibility, type of task and task parameters used for
- 8 studying associations with white matter parameters. Studies included in the main results provided
- 9 sufficient anatomical description/delineation of white matter tracts.

Results

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- 11 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
- 14 from diffusion MRI studies of healthy and clinical populations. For neuroimaging evidence, we
- 15 focused on studies using whole brain voxel wise analyses; studies using anatomical regions of
- interest (ROI) were selected according to methods and rationale.

17 Working memory

Causal evidence

- 19 Results from lesion studies and awake surgery have provided strong evidence for the role of the
- 20 superior longitudinal fasciculus (SLF), connecting the superior parietal to superior frontal lobes
- 21 longitudinally along the dorsal premotor and dorsolateral prefrontal regions ¹²³in working
- 22 memory. Kinoshita et al.¹²⁴ used voxel-based lesion-symptom mapping, DES and a visuospatial
- 23 2-back task paradigm to assess visuospatial working memory retrospectively and at least 6
- 24 months postoperatively in patients who underwent craniotomy under general anesthesia for right
- 25 prefrontal glioma. As compared with healthy controls and two patients who had undergone
- 26 awake surgery, the performance of patients operated under general anesthesia at follow-up
- 27 assessment was significantly lower, and correlated with lesions in the region overlapping the
- 28 SLF-I (dorsal part) and II (middle part). 125 These results agree with several findings pointing to a
- 29 major role for the SLF in supporting interactions among a right-lateralized system underlying

- 1 visuospatial attention^{75,126–128} within the D-FPN.⁷⁷ According to descriptions of functional
- 2 differentiation of its segments, ¹²⁸the SLF-I would be involved in the voluntary orienting of spatial
- 3 attention (i.e., the top-down, dorsal attention network)⁷⁵and the SLF-II would modulate
- 4 communication between the dorsal and ventral attention network, a system that directs attention
- 5 to spatial location of salient stimuli. 75,80
- 6 In a study of 29 patients undergoing awake surgery for removal of neoplastic lesions in the left
- 7 hemisphere, those performing the digit spans task while receiving DES in the left SLF-III (ventral
- 8 part) made order errors rather than item errors, but no language deficits were elicited. 129 The
- 9 authors propose that the SLF-III would underlie the transferal of order information from the
- 10 phonological store of the inferior parietal lobule to Broca's area, in other words, supporting the
- working memory phonological loop.⁵⁵
- 12 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
- 14 fronto-striatal tracts, in the left hemisphere. ¹³⁰Connecting 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
- 18 left FAT in language and in speech initiation. 133-135In the right hemisphere, its support of
- 19 executive functions has been hypothesized because it underlies a right-lateralized system
- 20 involved in cognitive control including the inferior frontal gyrus, the pre-SMA and subcortical
- 21 structures^{132,134,136} (i.e., regions integrating the L-FPN).⁷⁷One case report of awake surgery
- described the patient's inability to cite digits backwards during DES of the right FAT, whereas
- 23 digit spans forward were normally performed. 137 Associations with working memory would be
- 24 possible given the central role of the pre-SMA and SMA in verbal and non-verbal working
- 25 memory tasks.^{88,138,139}
- 26 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
- 29 subcortical-cortical modulation of goal-directed cognition and action, ^{136,141,142} the fronto-striatal
- 30 tracts could have at least an indirect role in the flexible manipulation of verbal information in

1 working memory.

Correlation evidence

3 In studies involving whole brain analyses of healthy individuals across ages 143-149 and in clinical

4 populations, 150,151 the integrity of the different segments of the corpus callosum (CC) has been

5 consistently associated with working memory assessed with different tasks. This was confirmed

6 in a study including a large group and controlling for multiple factors modulating performance,

7 including processing speed. 152 The CC genu, connecting symmetrical dorsolateral prefrontal

8 regions, 123 has been most consistently associated with working memory performance, in studies

9 exploring age-related decline in working memory performance. 143–145,147,148

perisylvian cortex of the frontal, parietal, and temporal lobes. 160

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. ¹⁵⁵Other 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

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

- 1 capacity and integrity of parahippocampal segments of the left cingulum, suggesting its support
- 2 of working memory.¹⁵⁶
- 3 Despite a hypothesized putative role of the FAT in executive functions, ¹³⁴ studies using whole
- 4 brain analyses did not report correlations. In ROI analyses restricted to language-associated
- 5 pathways, FA in the bilateral FAT has been correlated with performance in working memory in
- 6 healthy aging individuals. 153 Also, in a study exploring the functional differentiation of the FAT
- 7 in a larger sample, fiber density of its anterior right segments has been associated with n-back
- 8 performance, ^{163,164} with left segments correlated with language. ¹⁶⁴
- 9 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 system¹⁶⁰; the inferior
- longitudinal fasciculus (ILF), ¹⁵¹a ventral associative bundle connecting the occipital and temporal
- lobes; and the inferior fronto-occipital fasciculus (IFOF), ¹⁵¹connecting the ventral occipital lobe
- and the orbitofrontal cortex. 160
- 15 Results from studies of large groups of healthy individuals suggest the involvement of fibers
- 16 supporting cortico-subcortical networks in working memory performance. Some showed
- significant correlations with DTI metrics in the internal capsule (IC), ^{143,152} MD¹⁴⁷ and DKI¹⁴⁹
- indexes in the left superior and posterior corona radiata (CR). The IC and CR contain ascending
- 19 fibers from the thalamus to the cerebral cortex and descending fibers from the fronto-parietal
- 20 cortex to the subcortical nuclei. 160 Other studies showed significant correlations with MD and FA
- 21 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
- 23 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
- 25 in white matter microstructure, the integrity of the posterior thalamic radiation (TR), carrying
- 26 fibers between the thalamus and the PFC, was significantly correlated with working memory
- 27 performance in individuals with psychiatric disorders. 166

Summary

28

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

- 1 According to causal evidence, the left SLF-I was associated with verbal working memory¹³⁰;
- 2 more specifically, the left SLF-III would support the working memory phonological loop. 129 In
- 3 the right hemisphere, damage to the SLF-I and II induced impairment in visuospatial working
- 4 memory.¹²⁴ Diffusion MRI studies have shown converging results in different populations.
- 5 Although most DTI studies do not provide details on the segments of the SLF, causal and
- 6 correlation evidence indicate left lateralization for verbal and right lateralization for visual
- 7 working memory. 124,130,157
- 8 According to correlation evidence in large populations, the bilateral cingulum bundle, underlying
- 9 connections among salience nodes that integrate the M-CIN, ^{77,87} would support working memory
- 10 performance. 145,156,162
- 11 Causal evidence have shown that the disruption of the FAT would affect verbal working memory
- performance, with results for the left¹³⁰ and the right hemisphere. ¹³⁷ Diffusion MRI evidence
- 13 supporting these findings is scarce, based on ROI analyses and provided results for both
- 14 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
- 17 reported in DTI studies.
- 18 Results from diffusion MRI studies included in this review suggest a potential support of
- 19 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;
- 21 Supplementary Table 1)

22 **Set-shifting**

23

Causal evidence

- 24 Causal evidence indicated the involvement of the left SLF in performance on the TMT-B.
- 25 According to lesion analyses of cholinergic lateral pathways in 106 patients after acute and
- 26 chronic stroke, deficits were associated with damage to the left SLF. 167 Moreover, according to a
- 27 case report, post-operative damage to the SLF induced significant deterioration in TMT-B
- 28 shifting cost after surgical resection of a glioma located in the right hemisphere. Tractography
- 29 analysis revealed damage to the SLF-III, the AF and to a lesser extent the middle longitudinal

- 1 fasciculus and callosal fibers (tapetum); the SLF-I and II seemed relatively spared. 168 According
- 2 to the authors, deterioration in set-shifting abilities resulted from disruption of a cognitive control
- 3 network that spreads bilaterally in prefrontal but also cingular, parietal and temporal areas.⁸²
- 4 Indeed, the flexible switching between numbers and letters necessary for completing the TMT-B
- 5 also relies on working memory and visuospatial attention 169,170 and, in previous studies, both the
- 6 SLF-III and AF have been associated with visuospatial processing. 113,126
- 7 Results from the study of Cochereau et al. 140 are slightly different. In this large cohort, long-
- 8 lasting deficits on the TMT-B switch cost were prominently associated with post-surgical damage
- 9 to the left SLF-II.

10

Correlation evidence

- 11 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. ¹⁷⁴Such associations were not observed for gray matter ¹⁷⁴and remained
- strong after accounting for global white matter. 176
- 18 The anterior and posterior segments of the cingulum were strongly correlated with attention and
- 19 flexible responses in large groups of healthy aging adults, ^{162,179} with no associations found with
- 20 diffusivity or atrophy in cortical structures. ¹⁷⁹ Also, the cingulum, along with the CC and the SLF,
- 21 was associated with cognitive flexibility in persons with traumatic brain injury, suggesting its
- 22 involvement in cognitive control networks.¹⁷¹
- In two studies of healthy adults that used the TMT-B completion time¹⁷⁷ and switch cost¹⁷⁶ as
- 24 assessment parameters, the integrity of the left and right IFOF strongly predicted performance,
- 25 probably reflecting its implication in visually guided behavior. ¹⁸⁰
- 26 Regarding cortico-subcortical connections, results may vary depending on assessment methods
- and variables controlled. Analyses of clinical and healthy populations have shown associations
- 28 between low performance on set-shifting paradigms and low integrity of cortico-subcortical loops
- 29 with the pre-SMA and superior frontal gyrus, including clusters in the bilateral superior CR,
- 30 including the IC and posterior TR. 181,182 In studies using the TMT-B completion time, better

- 1 performance has been associated with better DTI parameters in the bilateral superior CR ¹⁷⁸;
- 2 right¹⁸³ and bilateral IC.¹⁸⁴ However, in analyses of more than 300 healthy aging adults,
- 3 correlations between the integrity of the left anterior TR and TMT-B completion time lost
- 4 significance after controlling for processing speed by means of different tasks. 185

Summary

5

- 6 Causal and correlation evidence have shown consistent associations between integrity of the SLF
- 7 and set-shifting performance. Severe decline of set-shifting abilities was prominently associated
- 8 with damage to the SLF-III and AF in the right hemisphere, but also the middle longitudinal
- 9 fasciculus and callosal fibers reflecting network disruption. ¹⁶⁸ In large populations, causal
- 10 evidence indicate that the left SLF, 167 and more precisely the left SLF-II, 140 supported better
- 11 performance. Convergent evidence from diffusion MRI studies in large populations agree with
- these findings, showing results for the left SLF¹⁷⁶ and left SLF-II.¹⁷⁴ Correlation studies exploring
- the CC showed frequent associations, especially with the genu^{143,171,172,186}
- 14 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
- 17 Regarding cortico-thalamic and cortico-striatal connections, DTI studies indicate the support of
- 18 the bilateral superior CR to flexible responses, within cortico-subcortical loops underlying
- 19 cognitive control. 181,182 (Fig. 2; Supplementary Table 1)

20 Inhibition

21

Causal evidence

- 22 Puglisi et al. assessed the feasibility of the Stroop task during awake surgery and showed that
- 23 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
- 26 months after resection. 187 In other analyses, the authors compared pre- and post-surgical
- 27 cognitive outcomes of 29 patients undergoing resection of a right frontal glioma, by using DES,
- 28 lesion-symptom mapping and diffusion tractography. DES of the anterior TR and fronto-striatal

- 1 tracts produced errors during the Stroop test, but results from lesion analyses showed that
- 2 inhibition was preserved in seven of eight patients with the inferior fronto-striatal tract spared. 188
- 3 However, overall differences before and after the surgery only approached significance and
- 4 showed slower performance rather than errors. Moreover, all patients had lesions in the right
- 5 hemisphere and were assessed only 1 month after surgery, which may be a short delay estimating
- 6 long-lasting impairments. 189 In larger groups of patients, with lesions in the right and left
- 7 hemisphere and at least 3 months after tumor resection, the Stroop interference index (i.e., time to
- 8 complete the interference minus the color-naming condition) was predominantly associated with
- 9 integrity of the SLF-II, to a lesser extent the SLF-III and weakly with fronto-striatal tracts, all
- 10 left-lateralized. 140
- 11 In the case report of Rutten *et al.* previously described, ¹³⁷ DES to the right FAT induced errors in
- 12 the Stroop task in a patient undergoing awake surgery for resection of a right frontal glioma;
- motor function was not disrupted.

Correlation evidence

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

- 21 Investigations of limbic-cortical networks and inhibition in small groups of people with
- 22 psychiatric disorders suggested the involvement of the cingulum, showing DTI metrics of FA and
- 23 MD associated with performance on the Stroop and Tower of Hanoi. 198,199 Convergent findings
- 24 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
- 28 consistently associated with performance on tasks assessing inhibition.
- 29 Results from studies of healthy and clinical populations using different tasks agree with

- 1 descriptions of a right-lateralized fronto-subcortical network supporting inhibition ^{132,136} with
- 2 convergent results for the right anterior TR. ^{203,202,197,191}In individuals with psychiatric conditions,
- 3 executive impairment has been associated with abnormal activation in cortico-subcortical
- 4 networks, ^{204–206} and low integrity of the right anterior IC. ²⁰⁴In line with these findings,
- 5 comprehensive analyses of neural correlates underlying cognitive control deficits have shown
- 6 reduced FA in the right anterior limb of the IC associated with impaired Stroop interference
- 7 index, along with abnormal activation of a right lateralized fronto-thalamo-cerebellar
- 8 network.²⁰⁷Similar associations have been reported in other populations, concerning the bilateral
- 9 anterior CR, bilateral anterior limb of the IC¹⁹⁰ and left EC.²⁰⁸

Summary

- 11 Results for inhibition points to a role for the CC, fronto-parietal and cortico-subcortical
- 12 connections. Convergent findings from causal and correlation evidence using verbal tasks
- 13 showed involvement of the left SLF. 140,194,195 More precisely, causal evidence in large
- populations showed results for the left SLF-II and III¹⁴⁰
- 15 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
- 18 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 within
- 20 the M-CIN network, engaged in salience detection and in maintaining task sets in demanding
- 21 cognitive tasks.⁷⁷
- 22 Causal evidence suggest the involvement of the right anterior TR in inhibition and showed
- 23 changes in performance associated with damage to the right inferior fronto-striatal tract. 188
- 24 However, these results have not been confirmed in analyses of long-term executive impairment
- 25 following tumor resection in large populations. ¹⁴⁰The diffusion MRI studies included in this
- 26 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
- 29 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

1 associations.(Fig. 2; Supplementary Table 1)

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Discussion 3 This review aimed to identify white matter tracts consistently associated with performance on 4 tasks assessing cognitive control abilities according to evidence from cognitive assessments 5 during intraoperative brain mapping, studies using lesion-mapping and diffusion MRI. As 6 expected, the CC was involved in all executive tasks, in different populations. Broadly and 7 according to how executive functions are most frequently assessed, 44 results point to several 8 white matter tracts, in particular those underlying fronto-parietal interactions, 98 within a network 9 in which the SLF would be the main connection. 10 Causal and correlation evidence showed bilateral contributions of the SLF to global executive 11 performance. 140,174,176,197 More precisely, the SLF was consistently involved in working 12 memory, ^{124,129,130,147,150,151,153–159} assessed with verbal and visual tasks; the left SLF-II supported 13 flexible responses 140,174; causal and correlation evidence showed left lateralization for tasks 14 assessing set-shifting and inhibition. 140,167,176 Moreover, convergent findings from diffusion MRI 15 studies have shown significant contributions of the cingulum bundle to cognitive 16 control. 162,171,179,198-201 To our knowledge, there is no causal evidence confirming findings for the 17 cingulum. This can be partly explained by the scarcity of studies using executive tasks while 18 performing brain mapping with DES and assessing associations between post-operative lesions 19 and long-term executive abilities. 211-213 20 Because subcortical structures modulate cortical responses, 136,142,214 the involvement of cortico-21 subcortical connections in cognitive control functions is expected. Several analyses indicate a 22 role for cortico-thalamic and cortico-striatal white matter, especially for the right anterior TR in 23 tasks assessing inhibition. 188,191,197,202,203 Other studies, including causal evidence showed the 24 involvement of the FAT and fronto-striatal tracts 130,137,140,164,188 in performance on executive 25 tasks. However, only one study¹⁴⁰ exploring associations with the FAT and fronto-striatal tracts 26 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. 29

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

The corpus callosum

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The CC is the largest commissural tract in the brain connecting left and right hemispheres. It 4 5 ensures interhemispheric transfer and integration of motor, sensory and cognitive information between homologous regions. It would also regulate homologous regions via an excitatory and 6 7 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 8 9 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 10 described according to topographical organization, including the genu, connecting symmetrical 11 dorsolateral prefrontal regions; the body, containing fibers connecting the premotor and 12 precentral frontal cortex; and the splenium, connecting occipital-temporal regions. 123 Studies of 13 patients with partial callosotomy showed functional differences of these subcomponents, its 14 posterior parts supporting visual, auditory and somatosensory information and anterior parts 15 supporting cognitive processes such as attention and executive functions. ²¹⁸ As expected, studies 16 included in this review have shown consistent support of the CC to all executive processes, 17 18 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 19 and right dorsolateral PFC, IFG and superior frontal gyrus, playing a critical role in such 20 abilities.²¹⁹ The unspecific but essential role of the CC has been further confirmed in DTI studies 21 22 showing independent contributions of the CC to executive performance and global cognition, 162,220-222 23

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 segments²²⁵ and functional differentiations. The SLF-I (dorsal part) connects parts of the superior parietal lobule

1 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 2 3 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 4 5 and prefrontal cortices. The SLF-III (ventral part) connects the inferior parietal lobule to the IFG, 6 extending from the rostral inferior parietal lobule to the ventral part of the premotor and 7 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 8 posterior temporal lobe. ^{223,225}A number of studies in the past decade have indicated the support of 9 SLF to a wide array of cognitive processes, from visual attention to language and complex 10 cognitive control processes. 95,110,113,126-128,226 11 12 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-13 mesial pathway, 110 whereas the SLF-III would support automatic capture of salient stimuli via a 14 ventral pathway. 128 The SLF-II would integrate information from the SLF-I and III, therefore 15 mediating interaction between dorsal and ventral attention systems. 128,223 Damage to this segment 16 in the right hemisphere induced left spatial neglect. 113,125 Beyond visuospatial attention, the right 17 SLF-II and III would also be involved in motor aspects of attention (i.e., visuomotor speed and 18 movement trajectory control) and bilaterally with cognitive aspects of motor function. ^{225,227}In 19 comprehensive analyses combining tractography and a meta-analytic approach to cluster fronto-20 parietal functions, the SLF-I was the main tract associated with spatial/motor clusters (e.g., 21 saccades, voluntary oriented attention) and the SLF-III, with non-spatial/motor clusters, (e.g., 22 verbal working memory, decision making); the SLF-II was associated with both.²²⁶ In line with 23 these descriptions, results from causal evidence included in this review have shown the support of 24 the right SLF-I and II to visuospatial working memory¹²⁴ and the left SLF-I to verbal working 25 memory. 130 Also, DES of the left SLF-III produced selective disruption of digit spans 26 27 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 28 by transferring order information from the phonological store to Broca's area. 129 The role of the 29 SLF and its different branches in language processes has been demonstrated. 95 The SLF-III is 30 thought to support phonological and articulatory processes according to causal evidence, 95,228 and 31

- 1 results of Papagno et al.¹²⁹ suggest a specific functional role of the SLF-III in verbal working
- 2 memory tasks. DTI studies have shown similar associations between the integrity of the left SLF
- 3 and performance on different verbal working memory tasks. 147,153,159 The SLF is indeed a major
- 4 connection underlying areas of activation during working memory tasks regardless of their
- 5 specific aspects and features, forming a "core" working memory network, including clusters in
- 6 frontal, parietal and insular cortices.⁸⁸

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- 7 According to results from causal and correlation evidence in large populations, the left SLF-II
- 8 would play a prominent role in flexible responses. 140,174 Strong evidence indicates a role for the
- 9 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
- 12 left SLF-II was strongly correlated with both measures and with global executive performance. 140
- 13 Causal evidence also showed that damage to the SLF-II, SLF-III and the AF disrupted
- 14 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
- 16 et al., 168 thus reflecting recruitment of visuospatial attention networks. Indeed, the role of the
- 17 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
- 19 Results from this review showed involvement of the SLF in all executive tasks, regardless the
- 20 parameters used to interpret performance across studies. Given that attentional processes are
- 21 essential for executive functions, the SLF is likely crucial because it supports the integration of
- 22 information within low top-down, visual, goal-oriented attention^{75,128,227} and cognitive control
- 23 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
- 27 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,
- 29 higher FA in the cingulum bundle independently contributed to better performance on the three
- 30 executive domains. 162 This complex white matter tract comprises short and long fibers that extend

1 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 2 3 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 4 cingulum have been described to improve the understanding of its potential underlying functions, 5 from two ("dorsal" and "ventral") to five subdivisions (subgenual, anterior, mideingulate, 6 retrosplenial, and parahippocampal or temporal). 161,229,230 Via a large fronto-parietal connectivity 7 within the cingulum, all of its components likely support interactions between working memory 8 and attentional resource allocation. 161 Results from this review suggest the involvement of its 9 bilateral anterior, posterior and left parahippocampal segments in verbal working memory. 145,156 10 studies have suggested its support of flexible responses and inhibition Several 11 abilities, ^{162,171,179,198,199,201} consistent with the previously described role of the anterior cingulate 12 cortex in error detection. 209,210 Moreover, the anterior/superior cingulum is connected to the 13 central precuneus, which has been recently shown to support set-shifting²³¹ and, more dorsally, is 14 likely a D-FPN node.⁷⁷ By supporting connections among key network nodes of salience 15 detection,⁸⁷ the cingulum bundle is probably an important connection underlying interactions 16 within the L-FPN and M-CIN networks.⁷⁷ Other studies are needed to increase knowledge about 17 the weight and specificity of cingulum contributions to executive functions, and describe possible 18 functional differentiations between its different segments. 19

The FAT and its putative role in cognitive control

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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. ¹³⁷Also, lesion analyses of large populations have shown results for verbal working memory, ¹³⁰moderate correlations between global executive performance but also verbal fluency, and damage to the FAT in the left hemisphere. ¹⁴⁰Regarding 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

- 1 cortex and the pre-SMA to the subthalamic nucleus, underlying the connectivity of a frontal-
- 2 subcortical network for response control. Given its connectivity with the IFG and cases of SMA
- 3 syndrome (reduction of spontaneous movement and speech function) after tumor resections, ⁹⁶
- 4 much of the research on the FAT has been related to language function, showing its support of
- 5 speech and language initiation, especially in the left hemisphere. ^{133,135,232}Recently, detailed
- 6 analyses showed a prominent role of the FAT in motor aspects of the language. ²³³However, such
- 7 associations are not restricted to the left hemisphere: some studies indicate the involvement of the
- 8 right FAT in stuttering and verbal fluency.^{234,235}
- 9 A role for the right FAT in executive functions has been hypothesized. 134 The pre-SMA and
- 10 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
- 16 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
- 19 cognitive control processes or if it would have an indirect role in executive performance via the
- 20 control of verbal responses.

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Cortico-striatal and cortico-thalamic connections

- 22 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
- 24 DES results from Puglisi et al.¹⁸⁸ differ from post-surgical assessments, in terms of tracts
- 25 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
- 27 performance of the Stroop task, but conclusions of lesion analyses in a subgroup of patients
- 28 describe a subtle slowing of performance only in those with the fronto-striatal tract resected.
- 29 Other results indicate a role for the fronto-striatal tracts in verbal working memory, along with
- 30 the FAT and the SLF¹³⁰ but also in global executive function in the left hemisphere. ¹⁴⁰ According

1 to a recent study using voxel-based lesion-symptom mapping in 36 patients who underwent 2 glioma resection in the right hemisphere, simultaneous damage of the middle cingulate cortex 3 and the fronto-striatal tract caused selective visual attention deficits, indicating that it could support attention control.²⁴⁰Nonetheless, the specificity of such associations remains unclear. 4 Damage to the fronto-striatal tract may affect cognitive control functions because it connects key 5 nodes supporting these processes; moreover, it has been involved in motor inhibition and 6 language initiation. 102,135,140 Analyses in large populations suggest that, in the left hemisphere, its 7 role is predominantly related to the verbal demands of executive tasks. 140 Concerning the right 8 anterior TR, DTI studies have shown converging findings suggesting its involvement in 9 performance on tasks assessing response inhibition.⁸⁻¹¹This is in line with a voxel-based lesion-10 symptom mapping showing that lacunar lesions located in the SLF and anterior TR were 11 associated with poor global executive function, 241 reflecting disruption of large-scale FPN-12 subcortical interactions. Moreover, the integrity of the right SLF-II and left anterior TR supported 13 better Common EF¹⁷⁴in analyses of the neural substrates underlying the unity/diversity model. 14 The question of whether the anterior thalamic radiations and fronto-striatal tracts are necessary 15 for normal cognitive control needs further investigation, but these convergent findings provide 16 strong evidence of their implication in executive functions. 17 Other results from DTI studies in large populations suggest that the EC, IC, CR are involved in 18 cognitive control processes 143,145,152,165,178,181,182,190,207,208 along with fronto-parietal connections 19 and the CC. Some studies showed contributions of these fibers to global executive function ^{208,242} 20 and in others, changes in activations of cortico-subcortical networks during task performance 21 supported such associations. 165,207 Collectively, causal and correlation evidence agree with 22 research describing thalamic modulation of functional connectivity across cortical regions, and 23 the role of thalamic nuclei in cognitive processes such as attention, behavioral flexibility and 24 more broadly, attentional control.^{67,243}As mentioned above, more than being relays of sensorial 25 information, basal ganglia structures have been identified as key nodes in neural models of 26 executive functions, ¹³⁶ supporting cognitive control within the L-FPN and the M-CIN networks. ⁷⁷ 27 Taken together, results from studies included in this review indicate the essential role of the 28 structural connectivity underlying the D-FPN, L-FPN and M-CIN networks in executive 29 30 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 31

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.⁷⁷The 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. 99At 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, of IFOF, one the the major mediating visuospatial association tracts awareness^{96,125,247,248}; language, ⁹⁵including lexical and semantic processing, ^{96,249}but also nonverbal 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. ¹⁷⁷These 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.

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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 networks and brain activity of specific also the interactions among 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

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- 1 indicating the tracts underlying the connectivity of well-described executive networks. Finally,
- 2 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
- 4 especially for complex and long connections that may induce specific deficits when damaged at
- 5 precise locations. ⁹⁶Concerning causal evidence, some conclusions remain limited because of the
- 6 scarce data from lesion analyses and DES results from the neuro-oncology field, regarding
- 7 executive functions.^{211,213}

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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 oncofunctional balance remains (i.e., the best trade-off between resecting the tumor and sparing functions). 256To 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. ²¹³Because 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.²⁵⁷These 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-
- 3 term survivors. ²⁵⁸ Several DTI studies exploring white matter in patients with brain tumor
- 4 revealed early microstructural changes after radiotherapy, which progressed over time and were
- 5 dose-dependent.^{259,260} Among these structures, the cingulum bundle was especially sensitive to
- 6 radiation-induced demyelination in white matter, ²⁶¹ so damage of this tract could participate in
- 7 the long-term cognitive decline observed in these patients. ⁶Knowledge of the role of white matter
- 8 tracts can contribute to the development of radiotherapy techniques²⁶² allowing to spare
- 9 functionally important white matter tracts, which seems a promising strategy to limit severe
- 10 cognitive disability in patients with brain tumor.

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Supplementary material

24 Supplementary material is available at *Brain* online.

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Figure legends

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

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- 20 Figure 2 Evidence of white matter tracts involvement in executive functions. Causal and
- 21 correlation evidence are represented for each executive process and white matter tracts. The
- 22 colors of the circles represent the total number of participants included in each study; the width of
- 23 the circles represent the number of included studies that reported significant associations
- 24 (Supplementary Table 1). The white matter tracts were generated from the Human Connectome
- 25 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
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- 1 corpus callosum; AF, arcuate fasciculus; SLF, superior longitudinal fasciculus; Cing, cingulum
- 2 bundle; FAT, frontal aslant tract; CST, cortico striatal tract; TR, thalamic radiation.

Box I 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 interference⁴³; 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. 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. 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. 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. 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.

There are several conceptualizations and different levels of complexity to describe executive functions. ⁴⁸⁻⁵¹The unity/diversity framework ⁴⁴contributed 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 sequencing⁵⁶ 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. S8.59 It encompasses several cognitive processes such as detecting salient stimuliand focusing on it, retaining relevant information and rules representations, and inhibiting previous responses according to the appropriate strategy. On the 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.

The Trail-Making Test B (TMT-B)⁶¹ and the Wisconsin Card Sorting Test⁶² 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} lt 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, an

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 anatomofunctional 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 Hospital production in the provide biological evidence in the provi

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 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. 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. The microstructural properties of brain tissue, especially for investigating the integrity of the myelin sheath or the axonal membrane. The microstructural properties of brain tissue, especially for investigating the integrity of the myelin sheath or the axonal membrane. The microstructural properties of brain tissue, especially for investigating the integrity of the myelin sheath or the axonal membrane. The myelin sheath or the axonal membrane model and 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

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



