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

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5 Damien Ricard<sup>2,8,9</sup>

6 **Abstract**

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

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  
24 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

4

## 5 **Introduction**

6 Complex and flexible cognitive processes are underpinned by widely distributed neural systems  
7 in the human brain,<sup>1-3</sup> 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  
11 information processing speed to high-level processes such as executive functions.<sup>4-6</sup>

12 Interest in white matter function has been increasing as conceptions of brain functioning have  
13 evolved from localizationist to network models. In localizationist models, brain functions are  
14 associated with and attributed to the activity of specialized brain areas,<sup>7</sup> whereas current  
15 conceptions describe brain functions emerging from flexible, dynamic and parallel interactions  
16 among distant and hierarchically organized networks of cortical and subcortical zones.<sup>2</sup>  
17 Descriptions of brain architecture and networks<sup>8-10</sup> have provided an account of brain network  
18 organization, properties and function not only at the cortical level but also in terms of subcortical  
19 connectivity.<sup>11,12</sup> More than just connectors, myelinated fibers reinforce the speed of conduction,  
20 and the connectivity of the white matter tracts allows the rapid synchronization of information  
21 among cortical regions.<sup>2,11,13</sup> 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.<sup>14</sup> According 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

1 brain injury,<sup>15–17</sup> multiple sclerosis<sup>18,19</sup> and cerebrovascular disease, for example.<sup>20</sup> Also,  
2 disconnection mechanisms and dysfunction of neural networks are thought to be involved in the  
3 marked executive and functional impairment associated with neuropsychiatric conditions such as  
4 major depression, bipolar disorder and schizophrenia.<sup>21,22</sup> White matter has been much studied in  
5 normal aging processes<sup>23</sup>: white matter microstructure damage and subsequent disconnection  
6 mechanisms are a central hypothesis explaining the decline or change in cognitive functioning.<sup>24–</sup>  
7 <sup>27</sup>Changes in brain architecture related to glioma growth and subsequent post-lesional  
8 neuroplasticity clearly revealed the key role of white matter, particularly regarding the dynamics  
9 underlying the flexible functioning and recovery potential of the central nervous system.<sup>28,29</sup>  
10 Diffuse low-grade gliomas develop slowly by infiltrating white matter. This induces neuro-  
11 synaptic reorganization and recruitment of adjacent or even contralateral zones for functional  
12 compensation of damaged areas, leading to significant changes in neural network architecture.<sup>30</sup>  
13 These changes give opportunities for optimal tumor resection, because resection boundaries can  
14 be defined according to individual perioperative responses triggered during direct electrical  
15 stimulation (DES),<sup>31</sup> as long as subcortical connectivity is identified and preserved.<sup>29,32</sup>  
16 Impairment of executive functions (Box 1) is indeed a common and perhaps a core deficit in  
17 brain conditions with predominant white matter damage.<sup>33–35</sup> Such deficits may severely  
18 compromise independence and quality of life because of their impact on professional, social, and  
19 emotional functioning.<sup>36</sup>

## 20 **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.<sup>72–75</sup> These regions form  
24 distinct neural systems with specific roles in directing the cognitive process toward the  
25 achievement of goal-directed behaviors.<sup>76</sup>

26 According to a review article that introduced a new taxonomy for the large-scale functional  
27 networks in the human brain,<sup>77</sup> 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  
30 visuospatial attention by preparing and exerting top-down selection for stimuli and responses.<sup>75</sup> It

1 includes the superior parietal lobule extending into the intraparietal sulcus, middle temporal  
2 complex and the putative frontal eye fields as core regions and would involve the ventral  
3 premotor cortex.<sup>74,75</sup> The L-FPN supports goal-directed control of information flow.<sup>78,79</sup> It  
4 comprises the lateral prefrontal cortex (PFC), along the middle inferior parietal lobule (including  
5 rostral and dorsolateral PFC) and the anterior inferior parietal lobule into the intraparietal sulcus  
6 as core regions, involving as well the midcingulate gyrus.<sup>80</sup> It has been described as a domain  
7 general system for a wide variety of demanding cognitive tasks.<sup>81,82</sup> Meta-analyses showed  
8 convergence of activations for the three executive domains in this system,<sup>83,84</sup> that has been  
9 associated with the common EF factor<sup>44,45</sup> in studies exploring the unity and diversity of the  
10 neural substrates of executive functions.<sup>85,86</sup> Also, the M-CIN, a right lateralized system, is  
11 thought to direct attention to spatial locations of salient stimuli and maintain task sets in  
12 demanding cognitive tasks. Core regions are the bilateral anterior insulae and anterior  
13 midcingulate cortex. Other involved regions are the inferior parietal cortex,<sup>80</sup> right temporal  
14 parietal junction and lateral PFC,<sup>75,79</sup> as well as subcortical structures including the basal  
15 ventromedial nucleus of the thalamus.<sup>72,77,87</sup>

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

31 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  
2 seen an increase in knowledge of the functional role of white matter tracts in motor, language,  
3 visuospatial processing and other cognitive processes, according to results from lesion studies  
4 and the neuro-oncology field.<sup>28,95–97</sup>The crucial role of the connectivity underlying the FPN for  
5 executive functions has been demonstrated in diffusion MRI and voxel-based lesion-symptom  
6 mapping studies.<sup>26,98,99</sup>However, studies exploring relations between white matter integrity and  
7 cognition usually report different groups of white matter bundles associated with performance on  
8 one or more cognitive tasks,<sup>100</sup> providing heterogeneous results. We still do not know whether  
9 specific tracts can prominently support executive functions (i.e., tracts consistently associated  
10 with executive functions across tasks, populations, and according to different levels of  
11 evidence).<sup>100</sup>

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

## 18 **Methods**

19 We searched PubMed for studies published from 2009 to 2023 that explored associations  
20 between executive functions and integrity of white matter tracts in healthy and cognitively  
21 impaired human adults. The searches were conducted using general and specific terms related to  
22 executive processes and techniques used to explore white matter. Executive tasks commonly used  
23 in clinical practice and research were included in the search terms, to retrieve studies that  
24 explored general cognition or used composite scores. We also included attentional processes to  
25 the search terms, to retrieve studies that explored attention using executive tests. The following  
26 terms were used: “anti-saccade”, “attentional control”, “attentional set shifting”, “cognitive  
27 control”, “executive functions”, “flexibility”, “inhibition”, “inhibitory control”, “interference  
28 control”, “selective attention”, “set shifting”, “sustained attention”, “task switching”, “updating”,  
29 “working memory”, “digit spans”, “n-back”, “Go No Go”, “Stop signal task”, “Stroop task”,  
30 “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,<sup>121</sup>using a checklist  
5 adapted from previous work.<sup>122</sup> (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.

## 10 **Results**

11 In the following sections, we summarize findings according to different levels of evidence, from  
12 causal to correlational: for each executive process, we present convergent findings for different  
13 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  
16 interest (ROI) were selected according to methods and rationale.

## 17 **Working memory**

### 18 **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<sup>123</sup>in working  
22 memory. Kinoshita *et al.*<sup>124</sup> 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).<sup>125</sup> 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<sup>75,126–128</sup> within the D-FPN.<sup>77</sup> According to descriptions of functional  
2 differentiation of its segments,<sup>128</sup> the SLF-I would be involved in the voluntary orienting of spatial  
3 attention (i.e., the top-down, dorsal attention network)<sup>75</sup> and 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.<sup>75,80</sup>

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.<sup>129</sup> The  
9 authors propose that the SLF-III would underlie the transfer of order information from the  
10 phonological store of the inferior parietal lobule to Broca's area, in other words, supporting the  
11 working memory phonological loop.<sup>55</sup>

12 Verbal working memory deficits have been associated with lesions in a crossroad of white matter  
13 pathways comprising the SLF (primarily branch 1) but also the frontal aslant tract (FAT) and  
14 fronto-striatal tracts, in the left hemisphere.<sup>130</sup> Connecting the inferior frontal gyrus with the  
15 anterior cingulate cortex and medial regions of the superior frontal gyrus (i.e., pre-SMA and  
16 SMA), the FAT has only recently been described<sup>131</sup> although previously identified in models of  
17 inhibitory control.<sup>132</sup> Evidence from DES and clinical studies points to a prominent role of the  
18 left FAT in language and in speech initiation.<sup>133–135</sup> In 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<sup>132,134,136</sup> (i.e., regions integrating the L-FPN).<sup>77</sup> One case report of awake surgery  
22 described the patient's inability to cite digits backwards during DES of the right FAT, whereas  
23 digit spans forward were normally performed.<sup>137</sup> 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.<sup>88,138,139</sup>

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

1 working memory.

## 2 **Correlation evidence**

3 In studies involving whole brain analyses of healthy individuals across ages<sup>143–149</sup> and in clinical  
4 populations,<sup>150,151</sup> 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.<sup>152</sup> The CC genu, connecting symmetrical dorsolateral prefrontal  
8 regions,<sup>123</sup> has been most consistently associated with working memory performance, in studies  
9 exploring age-related decline in working memory performance.<sup>143–145,147,148</sup>

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

25 The number of DTI studies presenting results for the cingulum bundle, connecting the cingulate  
26 cortex to numerous brain regions through short and long fibers,<sup>161</sup> is limited. However, working  
27 memory performance has been correlated with the integrity of this tract in large samples of  
28 healthy aging individuals.<sup>145,162</sup> One study showed the involvement of the bilateral anterior and  
29 posterior parts of the cingulum.<sup>145</sup> In smaller populations, analyses of training-induced plastic  
30 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.<sup>156</sup>

3 Despite a hypothesized putative role of the FAT in executive functions,<sup>134</sup> 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.<sup>153</sup> 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,<sup>163,164</sup> with left segments correlated with language.<sup>164</sup>

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

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  
17 significant correlations with DTI metrics in the internal capsule (IC),<sup>143,152</sup> MD<sup>147</sup> and DKI<sup>149</sup>  
18 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.<sup>160</sup> Other studies showed significant correlations with MD and FA  
21 in the external capsule (EC),<sup>145,165</sup> transporting fibers from prefrontal, temporal, SMA and pre-  
22 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  
24 striatum.<sup>165</sup> 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.<sup>166</sup>

## 28 **Summary**

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 memory<sup>130</sup>;  
2 more specifically, the left SLF-III would support the working memory phonological loop.<sup>129</sup> In  
3 the right hemisphere, damage to the SLF-I and II induced impairment in visuospatial working  
4 memory.<sup>124</sup> 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.<sup>124,130,157</sup>

8 According to correlation evidence in large populations, the bilateral cingulum bundle, underlying  
9 connections among salience nodes that integrate the M-CIN,<sup>77,87</sup> would support working memory  
10 performance.<sup>145,156,162</sup>

11 Causal evidence have shown that the disruption of the FAT would affect verbal working memory  
12 performance, with results for the left<sup>130</sup> and the right hemisphere.<sup>137</sup> Diffusion MRI evidence  
13 supporting these findings is scarce, based on ROI analyses and provided results for both  
14 hemispheres.<sup>153,164</sup> Likewise, causal evidence indicates a potential support of the fronto-striatal  
15 tract to a network involved in verbal working memory in the left hemisphere, along with fronto-  
16 parietal connections and the FAT,<sup>130</sup> 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  
20 and IC, along with the corpus callosum and fronto-parietal connections.<sup>143,145,152,165</sup> (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.<sup>167</sup> 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.<sup>168</sup> 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.<sup>82</sup>  
4 Indeed, the flexible switching between numbers and letters necessary for completing the TMT-B  
5 also relies on working memory and visuospatial attention<sup>169,170</sup> and, in previous studies, both the  
6 SLF-III and AF have been associated with visuospatial processing.<sup>113,126</sup>  
7 Results from the study of Cochereau *et al.*<sup>140</sup> 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  
12 populations<sup>171,172</sup> and in healthy individuals across ages.<sup>143,162,173,174</sup> Other studies indicated  
13 associations between better DTI metrics in the SLF and better performance on different tasks  
14 assessing set-shifting, based on switch costs<sup>171,175,176</sup> and TMT-B completion time.<sup>177,178</sup> More  
15 precisely, in large samples of healthy adults, axial diffusivity in the left SLF-II strongly predicted  
16 shifting-specific ability.<sup>174</sup> Such associations were not observed for gray matter<sup>174</sup> and remained  
17 strong after accounting for global white matter.<sup>176</sup>

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,<sup>162,179</sup> with no associations found with  
20 diffusivity or atrophy in cortical structures.<sup>179</sup> 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.<sup>171</sup>

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

26 Regarding cortico-subcortical connections, results may vary depending on assessment methods  
27 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.<sup>181,182</sup> In studies using the TMT-B completion time, better

1 performance has been associated with better DTI parameters in the bilateral superior CR<sup>178</sup>;  
2 right<sup>183</sup> and bilateral IC.<sup>184</sup> 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.<sup>185</sup>

## 5 **Summary**

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.<sup>168</sup> In large populations, causal  
10 evidence indicate that the left SLF,<sup>167</sup> and more precisely the left SLF-II,<sup>140</sup> supported better  
11 performance. Convergent evidence from diffusion MRI studies in large populations agree with  
12 these findings, showing results for the left SLF<sup>176</sup> and left SLF-II.<sup>174</sup> Correlation studies exploring  
13 the CC showed frequent associations, especially with the genu<sup>143,171,172,186</sup>

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

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.<sup>181,182</sup> (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  
24 insula and over the putamen induced task disruption, but patients made no errors in control tasks.  
25 In these patients, administration of the intraoperative Stroop task prevented executive deficits 3  
26 months after resection.<sup>187</sup> 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.<sup>188</sup>  
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.<sup>189</sup> 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.<sup>140</sup>

11 In the case report of Rutten *et al.* previously described,<sup>137</sup> 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;  
13 motor function was not disrupted.

#### 14 **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.<sup>190,162,191–193</sup> 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.<sup>184,194–197</sup>

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.<sup>198,199</sup> Convergent findings  
24 have been reported in other populations,<sup>162,200,201</sup> with its left posterior parts prominently  
25 associated with verbal rules (i.e., Stroop task) and its bilateral anterior parts sensitive to rule  
26 violations in the Tower of London task.<sup>200</sup>

27 Other tracts such as the fornix<sup>184,202</sup> and the uncinate fasciculus,<sup>195,201</sup> 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<sup>132,136</sup>with  
2 convergent results for the right anterior TR.<sup>203,202,197,191</sup>In individuals with psychiatric conditions,  
3 executive impairment has been associated with abnormal activation in cortico-subcortical  
4 networks,<sup>204–206</sup>and low integrity of the right anterior IC.<sup>204</sup>In 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.<sup>207</sup>Similar associations have been reported in other populations, concerning the bilateral  
9 anterior CR, bilateral anterior limb of the IC<sup>190</sup>and left EC.<sup>208</sup>

## 10 **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.<sup>140,194,195</sup> More precisely, causal evidence in large  
14 populations showed results for the left SLF-II and III<sup>140</sup>

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

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.<sup>188</sup>  
24 However, these results have not been confirmed in analyses of long-term executive impairment  
25 following tumor resection in large populations.<sup>140</sup>The diffusion MRI studies included in this  
26 review did not report associations between inhibition and integrity of the fronto-striatal tracts but  
27 several showed results for the right anterior TR.<sup>191,197,202,203</sup>

28 In line with the putative role of the right FAT in executive processes,<sup>134</sup> DES to the right FAT  
29 disrupted Stroop performance,<sup>137</sup> but this result has not been confirmed in post-lesional analyses  
30 of larger populations.<sup>140</sup> Diffusion MRI studies included in this review did not investigate such



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

2

### 3 **Discussion**

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

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

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

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.

### 3 **The corpus callosum**

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

### 24 **Consistent involvement of the SLF in executive functions**

25 Causal evidence from studies using DES and post-lesion cognitive assessment included in this  
26 review suggests that the SLF is a key white matter structure subserving executive processes  
27 <sup>124,129,130,140,167,168</sup> The SLF is a major association tract connecting lateral frontal, parietal and  
28 temporal cortical regions. Descriptions identify three<sup>223,224</sup> and others four segments<sup>225</sup> and  
29 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  
2 part of the premotor and prefrontal cortices. The SLF-II (middle part) connects regions around  
3 the intraparietal sulcus to regions in the superior and middle frontal gyrus including the frontal  
4 eye fields, extending from the caudal part of the inferior parietal lobule to the dorsal premotor  
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),  
8 connects temporal and parietal cortices, running posteriorly from the inferior parietal lobe to the  
9 posterior temporal lobe.<sup>223,225</sup> A number of studies in the past decade have indicated the support of  
10 SLF to a wide array of cognitive processes, from visual attention to language and complex  
11 cognitive control processes.<sup>95,110,113,126–128,226</sup>

12 In the right hemisphere, three branches of the SLF underlie a visuospatial network with distinct  
13 functional roles.<sup>128</sup> The SLF-I is thought to support goal-directed spatial attention via a dorsal-  
14 mesial pathway,<sup>110</sup> whereas the SLF-III would support automatic capture of salient stimuli via a  
15 ventral pathway.<sup>128</sup> The SLF-II would integrate information from the SLF-I and III, therefore  
16 mediating interaction between dorsal and ventral attention systems.<sup>128,223</sup> Damage to this segment  
17 in the right hemisphere induced left spatial neglect.<sup>113,125</sup> Beyond visuospatial attention, the right  
18 SLF-II and III would also be involved in motor aspects of attention (i.e., visuomotor speed and  
19 movement trajectory control) and bilaterally with cognitive aspects of motor function.<sup>225,227</sup> In  
20 comprehensive analyses combining tractography and a meta-analytic approach to cluster fronto-  
21 parietal functions, the SLF-I was the main tract associated with spatial/motor clusters (e.g.,  
22 saccades, voluntary oriented attention) and the SLF-III, with non-spatial/motor clusters, (e.g.,  
23 verbal working memory, decision making); the SLF-II was associated with both.<sup>226</sup> In line with  
24 these descriptions, results from causal evidence included in this review have shown the support of  
25 the right SLF-I and II to visuospatial working memory<sup>124</sup> and the left SLF-I to verbal working  
26 memory.<sup>130</sup> Also, DES of the left SLF-III produced selective disruption of digit spans  
27 performance, eliciting order rather than item errors. A similar disruption occurred when the  
28 supramarginal gyrus was stimulated, leading to the hypothesis of its role in the phonological loop  
29 by transferring order information from the phonological store to Broca's area.<sup>129</sup> The role of the  
30 SLF and its different branches in language processes has been demonstrated.<sup>95</sup> The SLF-III is  
31 thought to support phonological and articulatory processes according to causal evidence,<sup>95,228</sup> and

1 results of Papagno *et al.*<sup>129</sup> 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.<sup>147,153,159</sup> 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.<sup>88</sup>

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.<sup>140,174</sup> Strong evidence indicates a role for the  
9 left SLF-II and III in performance of tasks assessing flexibility and inhibition, according to  
10 analyses of resection cavities and disconnection probability in a large cohort of patients with  
11 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.<sup>140</sup>  
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  
15 attentional demands.<sup>140,168</sup> These were located in the right hemisphere in the study of Mandonnet  
16 *et al.*,<sup>168</sup> 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  
18 a large study exploring the impact of cardiovascular risk factors on cognition.<sup>98</sup>

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<sup>75,128,227</sup> and cognitive control  
23 networks (i.e., the D-FPN and L-FPN networks)<sup>75,77</sup> that is needed to goal-oriented behavior.

## 24 **Contributions of the cingulum bundle to executive functions**

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

## 20 **The FAT and its putative role in cognitive control**

21 According to direct in vivo evidence, the right FAT would be involved in executive functions,  
22 because DES of this white matter tract in the right hemisphere disrupted the manipulation of  
23 verbal information in working memory and inhibition of prepotent responses, whereas the  
24 performance of digit spans forward remained normal.<sup>137</sup> Also, lesion analyses of large populations  
25 have shown results for verbal working memory,<sup>130</sup> moderate correlations between global  
26 executive performance but also verbal fluency, and damage to the FAT in the left  
27 hemisphere.<sup>140</sup> Regarding DTI studies, there is limited evidence: two studies included in this  
28 review have suggested the involvement of the FAT in verbal working memory,<sup>153,164</sup> in one of  
29 them bilaterally.<sup>153</sup> The FAT was first detected in a study exploring brain structures involved in  
30 cognitive control. Aron *et al.*<sup>132</sup> 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,<sup>96</sup>  
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.<sup>133,135,232</sup> Recently, detailed  
6 analyses showed a prominent role of the FAT in motor aspects of the language.<sup>233</sup> However, 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.<sup>234,235</sup>

9 A role for the right FAT in executive functions has been hypothesized.<sup>134</sup> The pre-SMA and  
10 SMA subserve motor control, stopping behaviors and more specifically, conflict resolution  
11 between competing action plans<sup>68,236,237</sup> and have been identified as key nodes for verbal and non  
12 verbal working memory.<sup>88,138,139</sup> These structures and the right IGF would interact during context  
13 monitoring,<sup>46,238</sup> and the FAT would support these interactions within a broad cortico-basal  
14 ganglia-thalamic-cerebellar circuit involved in action control.<sup>134,239</sup> In line with this hypothesis,  
15 causal<sup>137,140</sup> and correlation evidence<sup>153,164</sup> showed its association with executive, goal-directed  
16 processes during verbal tasks. The FAT underlies connections among key nodes engaged in  
17 executive processes<sup>87,88,239</sup>; however, the current literature does not allow for inferences about  
18 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.

## 21 **Cortico-striatal and cortico-thalamic connections**

22 Several studies showed associations between executive functions and the integrity of tracts  
23 supporting of cortico-striatal and cortico-thalamic circuits, involved in the L-FPN and M-CIN.<sup>77</sup>  
24 DES results from Puglisi *et al.*<sup>188</sup> 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  
26 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 SLF<sup>130</sup> but also in global executive function in the left hemisphere.<sup>140</sup> 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  
4 support attention control.<sup>240</sup> Nonetheless, the specificity of such associations remains unclear.  
5 Damage to the fronto-striatal tract may affect cognitive control functions because it connects key  
6 nodes supporting these processes; moreover, it has been involved in motor inhibition and  
7 language initiation.<sup>102,135,140</sup> Analyses in large populations suggest that, in the left hemisphere, its  
8 role is predominantly related to the verbal demands of executive tasks.<sup>140</sup> Concerning the right  
9 anterior TR, DTI studies have shown converging findings suggesting its involvement in  
10 performance on tasks assessing response inhibition.<sup>8-11</sup> This is in line with a voxel-based lesion-  
11 symptom mapping showing that lacunar lesions located in the SLF and anterior TR were  
12 associated with poor global executive function,<sup>241</sup> reflecting disruption of large-scale FPN-  
13 subcortical interactions. Moreover, the integrity of the right SLF-II and left anterior TR supported  
14 better Common EF<sup>174</sup> in analyses of the neural substrates underlying the unity/diversity model.  
15 The question of whether the anterior thalamic radiations and fronto-striatal tracts are necessary  
16 for normal cognitive control needs further investigation, but these convergent findings provide  
17 strong evidence of their implication in executive functions.

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

28 Taken together, results from studies included in this review indicate the essential role of the  
29 structural connectivity underlying the D-FPN, L-FPN and M-CIN networks in executive  
30 functions. These networks very flexibly support a wide array of cognitive processes such as  
31 attentional control, selection and salience detection.<sup>77,244</sup> Complex responses emerge from the

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

31 There are limitations to this review. Although the cognitive tasks were included in different



1 sections (working memory, shifting, inhibition) according to their common use in clinical  
2 practice and research, such presentation of results could hinder the interpretations concerning  
3 other cognitive processes required for performing executive tasks. It is important to bear in mind  
4 that, although in theory there are separable executive constructs, executive processes interact with  
5 each other and tasks tap executive and non-executive processes (i.e., executive tasks are generally  
6 used as a proxy for one particular construct but may capture variance associated with several  
7 constructs).<sup>40</sup> For example, the integrity of projection fibers have been correlated with parameters  
8 of tasks or performance that also tap working memory capacity,<sup>170,252</sup> such as the TMT-B  
9 completion time,<sup>183,184</sup> and the Tower of London.<sup>202</sup> However, the objective of this review was to  
10 identify associations with tasks that are commonly used in the literature to assess cognitive  
11 control abilities. Considering the multifactorial aspects of executive tasks and the multiple  
12 functional roles described for some white matter tracts, overlapping is expected and the results of  
13 this review underline such aspect. Moreover, results were presented regarding the parameters  
14 used in the studies to interpret performance and other cognitive processes potentially involved.  
15 Other limits relate to technical aspects of each method used for the study of white matter and the  
16 availability of causal evidence. At the neural level, performance of executive tasks relies on the  
17 activity of specific brain networks and also the interactions among these  
18 networks.<sup>253,254</sup> Accordingly, the DTI studies selected in this review have shown different groups  
19 of white matter tracts associated with executive tasks. Our objective was to highlight consistent  
20 associations, but these are certainly more complex because a single tract can be correlated with  
21 multiple cognitive tasks and behaviors.<sup>100</sup> However, highlighting consistent findings may  
22 contribute to identifying not only tracts subserving multiple functions, but also those playing a  
23 less essential role that can be compensated for in case of a lesion.<sup>255</sup> Concerning diffusion  
24 weighted MRI studies, the sensitivity of the DTI metrics used as parameters for white matter  
25 integrity may be limited and hinder the identification of the spatial limits of white matter  
26 structures, especially white matter tracts containing “kissing” or crossing fibers.<sup>117,101</sup> Metrics  
27 derived from DKI seem to be more sensitive to changes in fiber diffusivity<sup>117,119</sup>; however, DKI  
28 is a time-consuming imaging technique mostly restricted to study protocols and not used in  
29 routine clinical practice. Only two studies included in this review used DKI to assess white  
30 matter tracts associated with specific executive tasks.<sup>149,158</sup> Nonetheless, several well-controlled  
31 studies including large samples have shown convergent findings, (Supplementary Table 1) thus

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  
3 described, such as the SLF<sup>123,160,223</sup> and the cingulum bundle.<sup>161,229,230</sup> This information is essential  
4 especially for complex and long connections that may induce specific deficits when damaged at  
5 precise locations.<sup>96</sup> Concerning 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.<sup>211,213</sup>

## 8 **Conclusions: clinical implications and perspectives**

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

1 In many cases, radiotherapy is an essential treatment for brain tumors but was found associated  
2 with radiation-induced cognitive decline after white matter damage in a subpopulation of long-  
3 term survivors.<sup>258</sup> 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.<sup>259,260</sup> Among these structures, the cingulum bundle was especially sensitive to  
6 radiation-induced demyelination in white matter,<sup>261</sup> so damage of this tract could participate in  
7 the long-term cognitive decline observed in these patients.<sup>6</sup> Knowledge of the role of white matter  
8 tracts can contribute to the development of radiotherapy techniques<sup>262</sup> 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.

11

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22

## 23 **Supplementary material**

24 Supplementary material is available at *Brain* online.

25

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## 17 **Figure legends**

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

19

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-](https://sites.google.com/a/labsolver.org/brain/diffusion-mri-templates/tractography)  
26 [templates/tractography](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.

### 4 **Box I Executive functions: conceptual framework and assessment**

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

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

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

#### 27 **Working memory**

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

36 Working memory and updating abilities are assessed with tasks such as digit-spans backwards, Wechsler Adult Intelligence Scale's letter-number  
 37 sequencing<sup>56</sup> and n-back tasks.<sup>57</sup>

#### 38 **Shifting**

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

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

#### 48 **Inhibition**

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

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

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

## 5 **Box 2 Techniques for the identification of white matter tracts and assessment of white matter** 6 **damage**

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

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

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

### 36 **Correlation evidence: neuroimaging techniques**

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

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

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



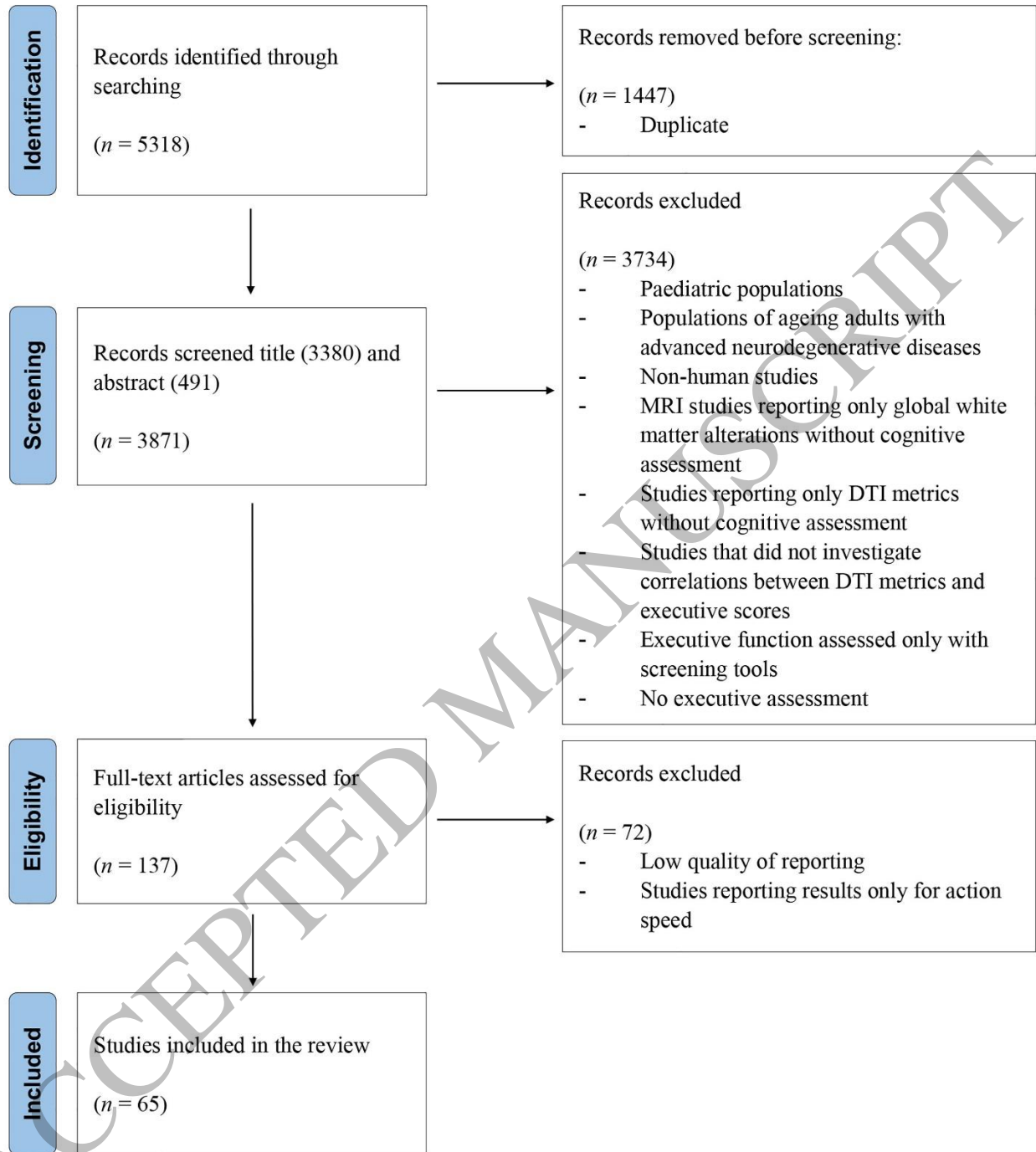
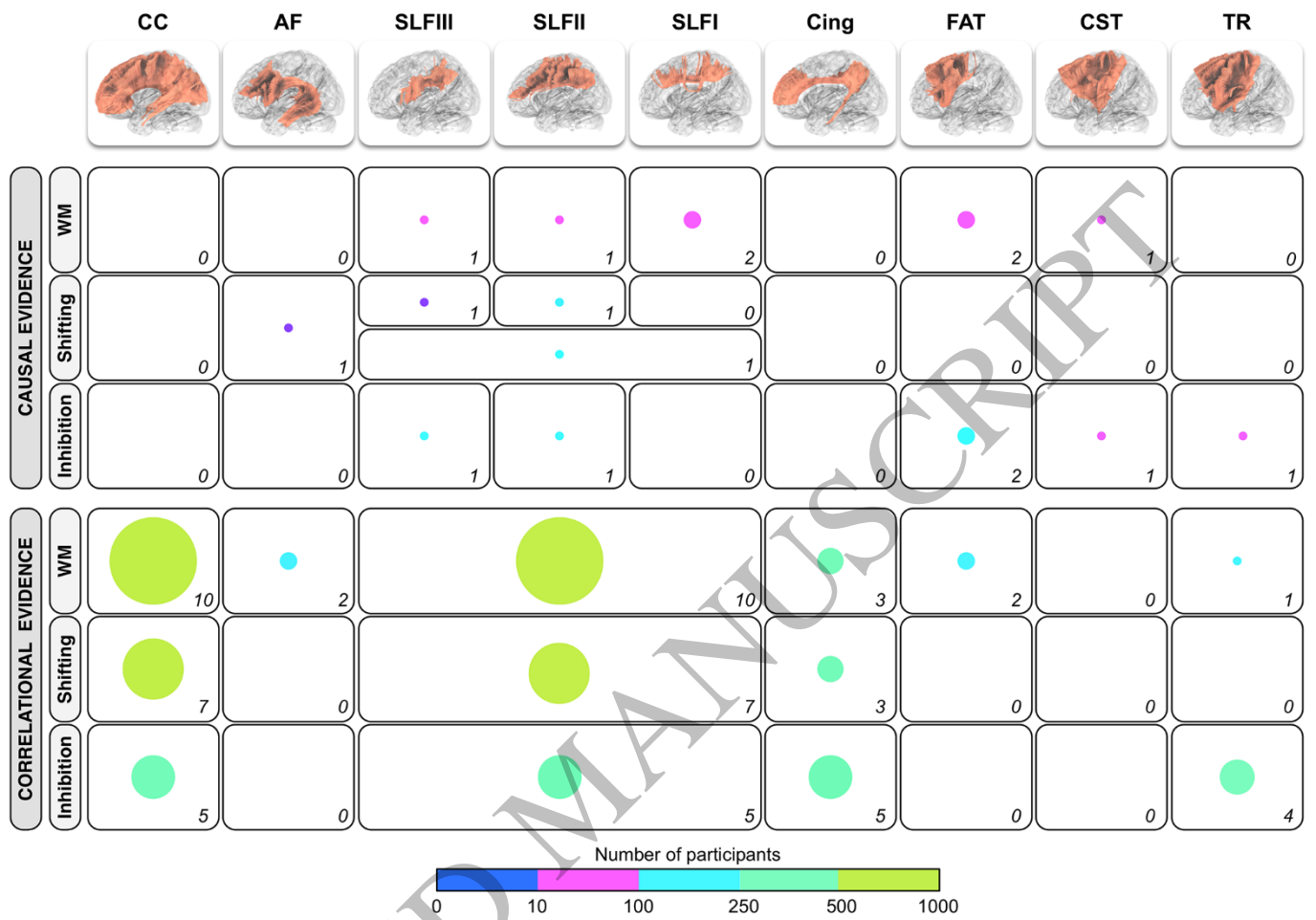


Figure 1  
500x559 mm ( x DPI)

1  
2  
3  
4



1  
2  
3

Figure 2  
180x128 mm (x DPI)