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Brain connectivity and cognitive processing speed in multiple sclerosis: a systematic review

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Abstract

Background: Processing speed (PS) decline is the most commonly observed cognitive deficit in people with multiple sclerosis (MS) resulting in a significant impact on quality of life. Despite its importance, knowledge of the underlying neural substrates is lacking.

Objective: As MS is increasingly recognised as a disconnection syndrome, our aim was to carry out a systematic literature review to clarify the relationship between PS performance and MRI measures of structural and functional brain connectivity in people with MS.

Search methods: A literature search was carried out on PubMed and Web of Science that included publications predating September 2017. Additional articles were added after inspection of the reference lists of all selected papers.

Data extraction: All selected papers were categorised in three sections according to the MRI measures investigated, independently or both. Quality assessment was carried out using a customised set of criteria.

Results: Thirty-two articles met the inclusion criteria and were included in the review. Microstructural integrity of the anterior corpus callosum and functional connectivity of frontal areas were more consistently found to correlate with PS performance, though high variability of findings was observed across studies. Several methodological flaws emerged from the reviewed literature.

Conclusions: Despite the observed trends, no definite conclusions can be drawn on the relationship between brain connectivity and PS decline in MS given the limitations of the current literature. Future investigations may benefit from theoretical and methodological advances to clarify how MS-related brain damage affects patients' cognition.

1. Introduction

Multiple sclerosis (MS) is an immune mediated disease characterised by an abnormal immune response targeting the central nervous system and causing both axonal demyelination and neuronal loss. The clinical course is variable, but can be categorised based on the degree of disease activity and disability progression rate into relapsing-remitting (RRMS), primary progressive (PPMS) and secondary progressive (SPMS) [1]. About 40 to 70% of people with MS experience cognitive impairment that may significantly impact both their quality of life and employment [2-5]. The cognitive domain that is most consistently affected in MS is processing speed (PS) [6,7]. PS is usually assessed by measuring the amount of information processed in a unit of time or the time needed to process a given amount of information [8,9].

Deficits in PS may have a broad influence on cognitive performance in people with MS. Indeed, memory and learning impairment is associated with impaired PS function [10-12]. Similarly, working memory and attention functions were predicted by performance in PS tasks that were also observed to be the best measure to discriminate people with MS from healthy controls [13-17].

Deficits in executive functions [18] and, more specifically, in planning [19,20] and interference inhibition on the Stroop test [21,22] are associated with PS across the various clinical courses of MS. Several studies investigated the impact of PS decline on cognition in people with MS. It was observed that in tasks of working memory [14,23], response inhibition [21], planning [20], task switching [24], and attention [25], after statistically controlling for PS performance, the differences between people with MS and healthy controls disappeared.

Despite extensive investigation into cognitive impairment in MS, its relationship with specific aspects of neural damage, especially in relation to PS function, is not clear yet. A meta-analysis of seven diffusion tensor imaging (DTI) studies found that cognitive decline in general was associated with lower fractional anisotropy, i.e. a measure of integrity of structural connectivity, in various tracts involved in different cognitive functions [26]. Another meta-analysis of thirty-nine studies [27] showed a strong correlation between measures of cognitive PS, namely the Paced Auditory Serial Addition Test (PASAT) and the Symbol-Digit Modalities Test (SDMT), and indices of white matter (WM) lesion volume and atrophy. However, most of the reviewed studies were carried out on samples of patients with mixed MS phenotypes using MRI measures that are global indicators of neurodegeneration and not linked to functionally defined brain regions. Only one study investigated the association between

MS lesion location and cognitive impairment and found that lesions occurred with greater frequency in the splenium and forceps major of the corpus callosum in cognitively impaired patients [28].
MS is increasingly recognised as a “disconnection syndrome” where widespread WM damage hampers communication between brain regions in a non-selective manner [29-35]. In line with this view the aim of the present review was to evaluate correlations between PS function in MS and measures of structural and functional connectivity.

2. Methods

A systematic review of neuroimaging studies investigating the relationship between indices of brain connectivity and performance on tasks of PS in MS was carried out. The specific aim was to summarise the current knowledge about the relationship between breakdown in brain connectivity and PS function in people with MS.
A literature search was undertaken in two online databases: PubMed and Web of Science. Studies using DTI and resting-state functional MRI (RS-fMRI) in combination with cognitive PS measures were specifically targeted. The exact strings searched are reported in Appendix A – Table A.1. No time limits were set and all the papers published up to September 2017 were assessed following the steps highlighted in the PRISMA statement (Figure) [36]. Additional papers from the reference lists of the selected articles that had not been identified in the literature searches were also included. After removal of duplicates, the full text of the remaining articles was inspected and paper selection was performed according to the following exclusion criteria: (1) review articles, (2) theoretical and/or modelling papers, (3) papers related to patients with pediatric-onset MS, (4) papers related to diseases different from MS, (5) animal studies, (6) biological studies, (7) pharmacological studies, (8) papers with no inclusion of PS measures, (9) papers with no use of either DTI or RS-fMRI techniques, (10) papers not in English.

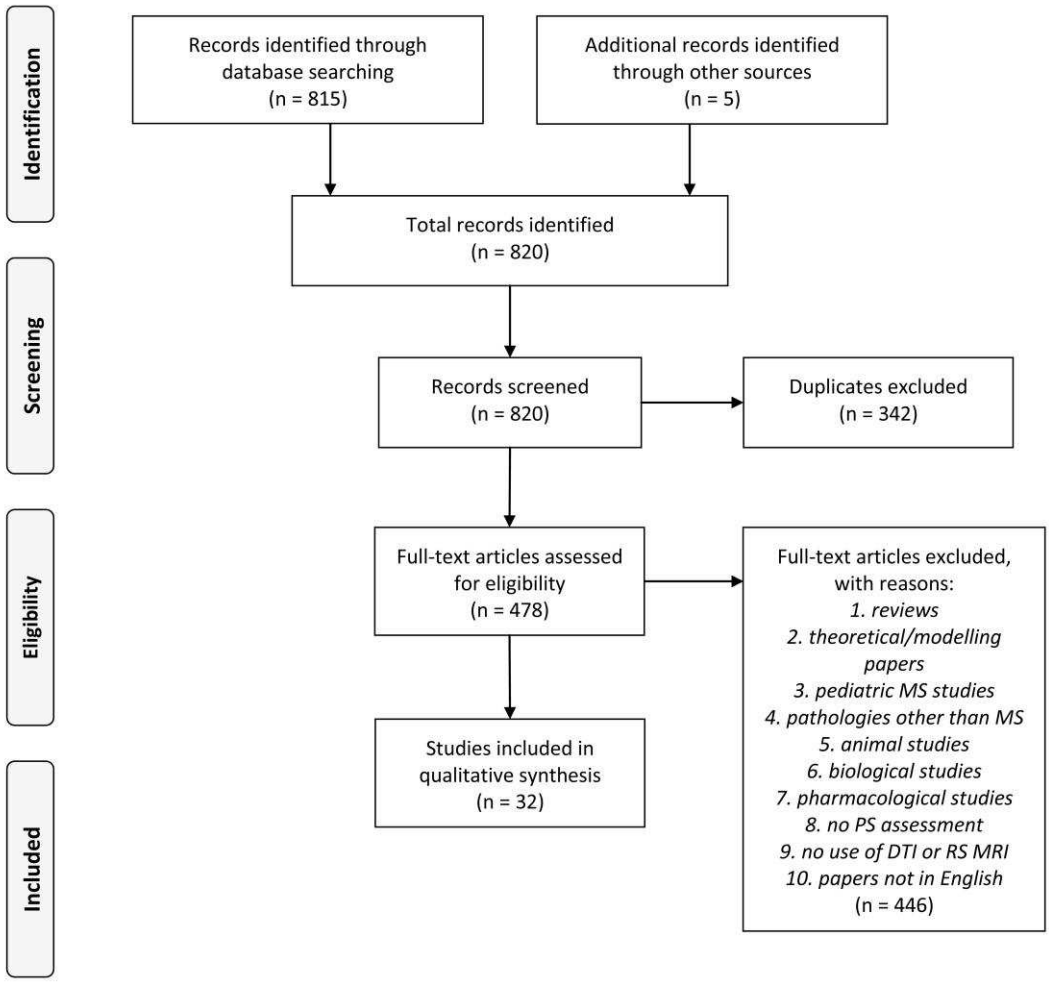

Figure 1 | Flow chart outlining the study selection process

Papers selected to be included in this review were assessed according to a customised set of criteria, adapted from those used by Welton and colleagues [26], that give an indication of their scientific quality and to ascertain possible sources of bias. A checklist of twelve questions was created and organised in five areas: methodology, clinical characteristics, MRI parameters, statistical analysis and results. Particular attention was given to the provision of details about the characterisation of the samples recruited and the analyses performed. A point was assigned for each quality criterion fulfilled. For the criterion assessing sample composition, 2 points were assigned to studies carried out on one or more groups of homogenous MS phenotypes, 1 to studies that included mixed phenotype samples, and no points to those reporting no information about phenotypes investigated. Therefore, the maximum score that could be achieved was 13 points. For more detailed information about quality assessment see Appendix B – Table B.1.

3. Results

A total of 820 papers were identified through online search and review of all the available references. Three hundred and forty-two entries were duplicates and the remaining 478 records were fully screened for eligibility. Thirty-two papers, all published between 2008 and 2017, met the final selection criteria to undergo review. Twenty-three studies reported the use of DTI measures to investigate structural connectivity only, 4 studies used RS-fMRI only for functional connectivity, and 5 studies combined DTI and RS-fMRI.

A summary of the quality assessment of the reviewed articles is reported in Table 1. Differences in the overall quality of papers between the three MRI categories were analysed using the Kruskal-Wallis test. The analyses showed the differences to be significant $\chi^2(2) = 6.497$, $p = .039$. After applying Dunn's multiple comparisons test, the only difference that remained significant was the one between studies using only DTI and those combining DTI with RS-fMRI ($p = .035$), with the latter showing higher scores (Figure 2). More detailed information on the evaluation of each quality criterion is reported in Appendix B – Tables B.2-B.4.

Table 1 | Descriptive statistics for the overall study quality assessment, categorised by MRI technique

MRI technique	Median	Interquartile range	Minimum	Maximum
DTI	9	4	4	12
RS-fMRI	10	6	6	12
DTI and RS-fMRI	12	3	10	13

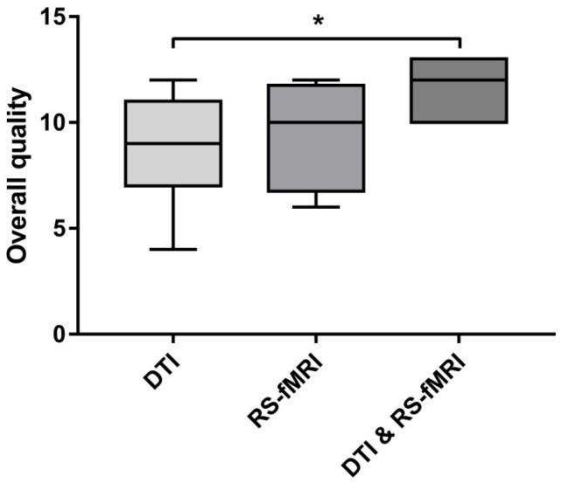

Figure 2 | Differences in the overall quality of reviewed papers

These findings show a gap in the overall scientific quality between DTI studies and those combining DTI with RS-fMRI measures. Arguably, this may be driven by technological advances and indeed studies using RS-fMRI were in general more recent than the DTI ones. However, it is also possible that studies combining several MRI techniques might have been more thoroughly designed. It must be noted, however, that only a few studies have been carried out with combined methodologies, thus making any conclusions not definitive.

3.1. Structural connectivity

Moderate heterogeneity was seen across studies with respect to sample composition, clinical information, analysis techniques, and covariates of no interest (Table 2). In particular, despite the fact that the majority of the studies investigated RRMS, eight included patients with different MS clinical courses without specific sub-sample analysis [37-44]. Progressive MS was underrepresented, with a single study on patients with SPMS [45]. Two papers were published on so-called “benign MS” [46,47], while one did not report explicitly the type of MS investigated [48].

In general, information on relapses and medications taken at the time of data collection were reported by most studies, but comorbidities and the presence or absence of fatigue and depressive symptoms were scarcely documented. This, together with lack of clearly stated a priori hypotheses lowered the quality of studies using only DTI measures compared to the others reviewed. There was, however, a trend towards improvement with better quality studies found in the most recent investigations of structural connectivity.

Statistical analyses were carried out with different approaches, the most common being the investigation of one or more regions of interest that was used in fourteen out of twenty-three studies [37,38,40,42-44,46,47,49-54]. The definition of the regions of interest was mainly a priori, though 2 studies defined them according to task-related functional activation [51] and differences in fractional anisotropy between MS patients and healthy controls [37]. Eleven out of twenty-three studies did not use multiple comparisons correction strategies [37,40,42,44,48-54] and twelve did not control for any covariate of no interest [38,39,42-44,48-54]. Among those publications that did, age was always included, followed by sex and premorbid cognitive status.

Table 2. Characteristics of studies on structural connectivity

Study	Sample	Age (years)*	Duration (years)*	EDSS*	PS measure	Covariates	Analysis	Results about correlations
Lin et al. 2008 **[49]**	36 RRMS: 9 CI 27 CP 13 HC	 37 (7.5) 37.7 (7.2) 34 (29-40)†	 10 (4.5) 7.2 (6.4)	 3.7 (1.5) 2.7 (1.2)	PASAT 3”	None	ROI of the CC	PASAT 3” negatively correlated with apparent diffusion coefficient in the CC
Roca et al., 2008 **[50]**	12 RRMS 12 HC	32.5 (8.0) 31 (8.5)	N.R.	< 2	PASAT 3”	None	ROIs: FL, FM, OF, cingulate	PASAT 3” positively correlated with FA only in the FL region
Bonzano et al., 2009 **[51]**	23 RRMS 18 HC	32.5 (4.2) n.r.	6.9 (3.2)	1.6 (0.8)	PVSAT-100	None	ROI of the left SLF	PVSAT-100 positively correlated with mean FA in the left SLF
Dineen et al., 2009 **[29]**	41 RRMS 27 HC	43.5 (31-56)† 36.4 (28-55)†	10.5 (3-28)†	3 (1.5-6.5)†	PASAT 3”	Age, IQ, EDSS	TBSS	PASAT 3” positively correlated with FA in the CC, left SLF and cingulum, right ILF, and bilateral AF and optic radiations
Mesaros et al., 2009 **[47]**	54 BMS 21 HC	46.4 (35-63)‡ 45.7 (25-66)‡	22.5 (15-39)‡	1.5 (0-3)‡	PASAT 3”	Age, sex	ROI of the CC	PASAT 3” positively correlated with mean FA and negatively with mean MD in the CC
Roosendaal et al., 2009 **[37]**	30 MS: 5 CIS 21 RRMS 4 SPMS 31 HC	40.6 (9.1) 40.6 (9.9)	3.6 (3.5)	3 (0-6.5)†	LDST	Age	ROI of clusters of lower FA: MS < HC	LDST positively correlated with mean FA and negatively with mean RD in the left body of the CC
Warlop et al., 2009 **[48]**	15 MS	37.6 (21-49) ‡	5.1 (3.4)	2.5 (2.2)	PASAT 3” SDMT	None	Whole brain	PASAT 3” not correlated with any measure; SDMT negatively correlated only with global RD
Ozturk et al., 2010 **[38]**	69 MS: 35 RRMS 20 SPMS 14 PPMS 29 HC	45 (22-66)‡ 40 (22-58)‡ 51 (40-66)‡ 50 (29-66)‡ 34 (22-63)‡	10 (0-42)‡ 6 (0-22)‡ 19 (4-37)‡ 8 (1-42)‡	3.5 (0-7)‡ 3 (0-6)‡ 6.5 (3.5-7)‡ 3.5 (1.5-6.5) ‡	PASAT 3”	None	ROI of the CC	PASAT 3” positively correlated with mean FA in the CC, especially anterior body, in all MS phenotypes
Van Hecke et al., 2010 **[39]**	20 MS: 10 LD 10 HD 10 HC	 43 (9) 41 (7) 42 (10)	 12 (7) 11 (5)	 2 (1) 6 (1)	PASAT 3”	None	Voxel-wise	PASAT 3” correlated with FA, MD and RD in: left cingulum and ILF, bilateral CR, FMI, genu of the CC, SLF, interna and esterna capsulae

Table 2 (continued)

Study	Sample	Age (years)*	Duration (years)*	EDSS*	PS measure	Covariates	Analysis	Results about correlations
Rimkus et al., 2011 **[52]**	23 RRMS 13 HC	31.9 (9.2) 27.7 (5.4)	2.4 (1.4)	1.4 (1.2)	SDMT TMT	None	ROI of the CC	SDMT negatively correlated with mean FA of the CC; TMT not correlated with any measure
Llufriu et al., 2012 **[53]**	21 RRMS 12 HC	37.2 (6.9) 35.2 (7.4)	9.5 (5.4)	2 (0-6)†	PASAT 3” SDMT	None	ROI of the CC	PASAT 3” and SDMT not correlated with any measure
Yu et al., 2012 **[55]**	37 RRMS 20 HC	40.9 (10.1) 34 (10.3)	9.3 (9.5)	2.2 (0-4)†	PASAT 3” SDMT	Age	TBSS	PASAT 3” positively correlated with FA in: right PTR, right SS and CC; SDMT positively correlated with FA in: CC, right CR and cingulum, left external capsule, bilateral PTR, SS and UF
Benedict et al., 2013 **[40]**	75 MS: 50 RRMS 24 SPMS 18 HC	46.4 (9) 42.1 (11.5)	11. (7.5)	3.5 (0-6.5)†	PASAT 3” SDMT	Age, education	TBSS and ROI of the thalamus	Mean thalamic MD was third predictor, after age/education and thalamic volume, of scores on PASAT 3” and SDMT
Bester et al., 2013 **[46]**	26 BMS 24 HC	53.4 (7.1) 51.6 (11.2)	25.8 (9.6)	1.5 (0-3)†	PASAT 3” SDMT	Age, sex	ROIs: CC and ATR	PASAT 3” and SDMT not correlated with FA and MD either in the CC and the ATR bilaterally
Bozzali et al., 2013 **[56]**	25 RRMS 25 HC	34.5 (8.6) 31.8 (8.1)	7 (2-16)†	2 (0-4.5)†	PASAT 3”	Age, sex, T2-LL, n. of voxels	TBSS and ACM	PASAT 3” positively correlated with ACM in: anterior CC, IX cerebellar lobule bilaterally, and right hippocampus
Genova et al., 2013 **[41]**	25 MS: 22 RRMS 2 SPMS 1 PPMS 15 HC	44 (7.9) 36.3 (10.3)	9.6 (7)	N.R.	TMT-A CWIT	Age	TBSS	TMT-A positively correlated with FA in: left body and splenium of the CC, left IFOF, right FMI and PTR, bilateral CR, FMA and SLF; CWIT positively correlated with FA in: left body of CC, right ATR, PTR, splenium and FMI, bilateral fornix and SLF
Mazerolle et al., 2013 **[57]**	20 RRMS 20 HC	42.4 (6.3) 42.5 (7.8)	8.1 (6.9)	2.2 (0-6)†	SDMT	Age	TBSS	SDMT correlated positively with FA and negatively with MD/RD in: body and genu of CC, PTR, SLF; no correlations with AD
Sbardella et al., 2013 **[58]**	36 RRMS 25 HC	34 (8) 31 (6)	7.4 (6.1)	2.5 (1-4.5)†	PASAT 2” PASAT 3”	Age, sex, T2-LL	TBSS	PASAT 2” correlated positively with FA in widespread WM tracts and negatively with MD in right cerebral peduncle, right ILF, and left cingulum; PASAT 3” not correlated with any measure

Table 2 (continued)

Study	Sample	Age (years)*	Duration (years)*	EDSS*	PS measure	Covariates	Analysis	Results about correlations
Koenig et al., 2014 **[42]**	53 MS: 45 RRMS 7 SPMS 20 HC	44.3 (8.9) 41.3 (9.7)	8 (1-33)†	1.5 (1-6.5)†	PASAT 3” SDMT	None	ROI of the fornix	PASAT 3” not correlated with any measure; SDMT correlated with all diffusion measure of the fornix, more strongly on the left side
Kern et al., 2015 **[54]**	27 RRMS 20 HC	37.9 (8.2) 34.1 (9.4)	N.R.	2.5 (1.1)	PASAT and SDMT combined	None	ROIs: cingulum, fornix, UF	Mean FA of bilateral UF significantly predicted PS performance; mean RD of bilateral UF correlated with PS scores
Koenig et al., 2015 **[43]**	57 MS: 44 RRMS 13 SPMS 17 HC	44.6 (8.4) 42.7 (10.1)	11 (1-33)†	2.5 (1-6.5)†	PASAT 3” SDMT	None	ROIs: posterior cingulum, PLIC	PASAT 3” not correlated with any measure; SDMT negatively correlated with MD and RD (mean of left and right) in PLIC and posterior cingulum
Meijer et al., 2016 **[45]**	30 SPMS: 12 CI 18 CP 32 HC	 51.9 (8.1) 55 (7.4) 40.6 (12.9)	 19.3 (8-30)† 25 (9-48)†	 6.5 (4-8.5)† 6.2 (5.5-8.5)†	PASAT 3” SDMT combined to assess CI	Age, sex, IQ	TBSS	Global mean RD significantly predicted global cognitive impairment
Moroso et al., 2017 **[44]**	37 CIS 32 MS 36 HC	36 (19-59)† 42 (29-59)† 36 (21-60)†	4.25 (1.98)# 106.11 (61.44)#	1 (0-6)† 3 (0-8)†	SDMT	None	ROIs: cerebellar peduncoli, VI, VIIb, VIIIa, VIIIb, crus I, and crus II lobules	SDMT correlated positively with FA in the left VI, the right VIIIa and VIIIb lobules, middle and inferior cerebellar peduncles; SDMT correlated negatively with MD in the vermis crus II, middle and left superior cerebellar peduncles

ACM: anatomical connectivity maps, AD: axial diffusivity, AF: arcuate fasciculus, ATR: anterior thalamic radiations, CC: corpus callosum, CI: cognitively impaired, CP: cognitively preserved, CR: corona radiate, CWIT: Colour Word Inhibition Test, EDSS: Expanded Disability Status Scale, FA: fractional anisotropy, FL: fronto-lateral, FM: fronto-medial, FMA: forceps major, FMI: forceps minor, HC: healthy controls, ILF: inferior longitudinal fasciculus, IFOF: inferior fronto-occipital fasciculus, IQ: intelligence quotient, LDST: Letter Digit Substitution Test, MD: mean diffusivity, OF: orbito-frontal, PASAT: Paced Auditory Serial Addition Test, PLIC: posterior limb of the internal capsule, PPMS: primary progressive multiple sclerosis, PTR: posterior thalamic radiations, PVSAT: Paced Visual Serial Addition Test, RD: radial diffusivity, ROI: region of interest, RRMS: relapsing-remitting multiple sclerosis, SDMT: Symbol-Digit Modalities Test, SLF: superior longitudinal fasciculus, SPMS: secondary progressive multiple sclerosis, SS: sagittal stratum, T2-LL: lesion load on T2 images, TBSS: tract-based spatial statistics, TMT: Trail Making Test, UF: uncinate fasciculus, WM: white matter

N.R. = not reported
* Mean (SD)
† Median (Range)
‡ Mean (Range)
§ Mean only
# Duration in months

The most consistent difference observed between people with MS and healthy controls in DTI studies was the presence of abnormalities in the corpus callosum. This interhemispheric bundle of fibres appeared to be particularly affected by MS pathology. Additionally, other WM tracts also showed abnormalities including: the superior and inferior longitudinal fasciculus, the cingulum, and the fornix. Most of these are associative WM tracts that mainly support different cognitive functions.

Weak or absent correlation between DTI indices and PS measures was reported in five papers using the PASAT, in particular the 3 sec version (PASAT 3") [42,43,46,53,58]. This finding, in line with the aforementioned review on atrophy measures [27], may be due to a lower PS load of the 3 sec version compared to more challenging versions of the same test or to the SDMT. Indeed, Sbardella et al. [58] observed that the PASAT 2", but not the PASAT 3", significantly correlated with both fractional anisotropy and mean diffusivity in a widespread network of WM tracts centred on the right inferior longitudinal fasciculus and the left cingulum. While Sbardella and colleagues [58] used a tract-based spatial statistics approach to investigate voxel-wise associations within a skeleton of WM containing only the core of the tracts, lack of correlation between the PASAT 3" and DTI indices was otherwise observed in studies of patients with different MS phenotypes utilising either whole-brain global indices [48] or several regions of interest: anterior thalamic radiations [46], corpus callosum [46,53], fornix [42], posterior cingulum and posterior limb of the internal capsule [43].

In line with the findings from comparisons between people with MS and healthy controls, in studies with mixed MS phenotypes, the corpus callosum was the WM bundle most commonly reported to be correlated with the PASAT 3", both in region-of-interest [38,47,49] and voxel-wise investigations [29,39,55,56]. However, performance on this test was also noted to correlate with the degree of microstructural integrity of other WM tracts, mainly: the left cingulum [29,39,58]; the superior longitudinal fasciculus, especially on the left side [29,39,51]; and the inferior longitudinal fasciculus bilaterally [29,39,58]. Moreover, less consistent associations with the PASAT were detected in the arcuate fasciculus [29], right posterior thalamic radiations and right sagittal stratum [55], hippocampal and cerebellar WM [56], the lateral portion of the frontal lobes [50], and with thalamic mean diffusivity [40]. Only one study found that microstructural integrity of the bilateral uncinate fasciculi predicted PS performance assessed combining the PASAT and the SDMT [54].

The only study carried out on SPMS did not investigate PS as a distinct domain but divided the patients' sample into cognitively impaired and preserved sub-samples, based on performance on

various tests, among which were the PASAT and the SDMT. Mean global radial diffusivity, among the different DTI measures, emerged as the only significant predictor of cognitive status. However, all DTI indices were found to be significantly different between cognitively impaired and cognitively preserved groups in: the fornix, the superior longitudinal fasciculus, and the forceps major [45].

In contrast, fewer studies investigated the association between structural connectivity measures and performance on the SDMT in people with MS. Among them, only two failed to report any significant correlation in two regions of interest, namely anterior thalamic radiations [46] and the corpus callosum [46,53]. Similar to the results on the PASAT, higher structural integrity of the corpus callosum, particularly in the body, also appears consistently linked to higher scores obtained on the SDMT [52,55,57] and a similar test of visual PS: the Letter Digit Substitution Test [37]. However, DTI indices were more often observed to be correlated with this test in other WM fibre bundles: the fornix, both left-lateralised [42] and bilaterally [55]; the cingulum, on the right side [55] and globally [43]; and the posterior thalamic radiations bilaterally [55,57]. Less commonly, significant correlations between the SDMT scores and DTI measures were additionally detected by region-of-interest and voxel-wise analyses in: the posterior limb of the internal capsule [43], thalamus [40], bilateral uncinate fasciculi, sagittal stratum [55], and the superior longitudinal fasciculus [57].

Only two DTI studies investigated the Trail Making Test: the first [52] reported no correlation in the region of interest of the corpus callosum, while a voxel-wise study found that performance on this test was correlated with fractional anisotropy in different parts of the corpus callosum, the left inferior fronto-occipital fasciculus, right posterior thalamic radiations, and bilateral superior longitudinal fasciculi [41]. This latter study also found that a PS index derived from the Stroop test correlated with structural connectivity integrity of the corpus callosum, bilateral fornix, and right-lateralised anterior and posterior thalamic radiations.

3.2. Functional connectivity

Four studies focussed solely on resting-state brain activity and its relation to PS ability in RRMS (Table 3). Patients' age, duration and severity were quite similar across studies and, in general, the reported clinical data were more detailed than in DTI studies although details about relapses were missing [30,59]. While most studies investigated different cortical and subcortical regions of interest, one study analysed functional connectivity within the graph theory framework by dividing the brain into

116 grey matter (GM) areas, extracting the average resting-state signal from each area, and finally calculating linear correlation between signals from each pair of GM areas [30]. The majority of the studies did not use statistical correction for multiple comparisons [30,31,60] and only two controlled for possible confounding variables [31,60]. However, studies on functional connectivity were of a slightly higher, although not significant, quality compared to the structural connectivity studies, given that all were explicitly hypothesis-driven with just one exception [60] (Appendix B – Table B.3). The PASAT 3" was the most commonly used test of cognitive PS function, although mainly in combination with other tasks, which resulted in high variability of PS assessment across studies [30,59].

When functional connectivity was compared between people with MS and healthy controls, reductions were reported in the somatosensory network, medial and lateral visual networks [59], and between posterior and anterior cingulate cortex and right inferior frontal gyrus [60]. Consistently, graph-based analysis of functional connectivity revealed how the brains of people with MS tend to reorganise and become more modularised. This means that connectivity between brain areas that are functionally related to one another and form a module tends to increase in MS, while functional connectivity between areas belonging to different brain modules becomes weaker [30]; (see Fleisher et al. [61] for a recent review of graph theory and brain networks in MS). These findings support the view of MS as a disconnection syndrome due to different functionally related areas becoming more independent from one another and, in turn, hampering information integration across the brain.

Accuracy in a dual-task PASAT 3" was reported to be negatively associated with the general level of network modularity (i.e. reduced between-network connectivity) characterising brains affected by MS: the higher the brain modularisation the worse the PS performance [30]. Wojtowicz et al. [60] also found that the higher the intra-individual variability in the semantic search reaction time task of the Computerised Test of Information Processing, the lower the functional connectivity between ventro-medial prefrontal cortex and the left frontal pole. No alterations in connectivity of the ventro-medial prefrontal cortex were reported between people with MS and healthy controls, however.

Table 3. Characteristics of studies on functional connectivity

Study	Sample	Age (years)*	Duration (years)*	EDSS*	PS measure	Covariates	Analysis	Results about correlations
Janssen et al., 2013 **[59]**	28 RRMS 28 HC	46.4 (8.8) 45.6 (9.2)	10.6 (5)	3.9 (1.2)	Composite score: PASAT 2", PASAT 3", LCT, PCT	None	ROIs: 6 RS networks	Composite score not correlated with FC of any of the 6 networks
Gamboa et al., 2014 **[30]**	16 MS: 8 CIS 8RRMS 20 HC	35.3 (8.3) 29.9 (7)	N.R.	≤ 2.5	Dual task PASAT 3"	None	Modularity of the global FC network	Accuracy in the dual task PASAT 3" correlated with global network modularity
Wojtowicz et al. 2014 **[60]**	18 RRMS 16 HC	42.1 (7.4) 43.1 (7.8)	7.5 (1-28)†	2.2 (1-3.5)†	CTIP	ISD of RT	ROI: DMN	ISD on the SSRT negatively correlated with FC between vmPFC and left frontal pole
Pravatà et al., 2016 **[31]**	22 RRMS: 11 NF 11 WF 12 HC	 40 (5.8) 46.6 (9.3) 41.4 (8)	 6 (4.4) 9.5 (3.8)	 1.4 (0-3)† 2.5 (0-3.5)†	PASAT 3"	EDSS, duration	ROIs: SFG, caudate, thalamus	PASAT 3" not correlated with FC of the left SFG, but positively correlated with post-performance decrease in FC between the left SFG and the left thalamus

CIS: clinically isolated syndrome, CTIP: Computerised Test of Information Processing, DMN: default mode network, FC: functional connectivity, ISD: individual standard deviation, LCT: letter comparison task, NF: not fatigued, PCT: pattern comparison task, ROI: region of interest, RRMS: relapsing-remitting multiple sclerosis, RS: resting state, RT: reaction time, SFG: superior frontal gyrus, SSRT: semantic search reaction time, vmPFC: ventro medial prefrontal cortex, WF: with fatigue

N.R. = not reported
* Mean (SD)
† Median (Range)

Another region-of-interest study compared functional connectivity changes between a baseline scan acquired just before in-scanner performance of two consecutive blocks of the PASAT 3" and two subsequent scans: one acquired just after completion of the second block and one after 30 minutes. The scores on the PASAT 3" correlated with the decrease of connectivity occurring in the 30 minutes after task performance between the left superior frontal gyrus and the left thalamus [31]. However, PS function was not correlated with functional connectivity of the left superior frontal gyrus at baseline. Finally, Janssen and colleagues [59], instead, calculated a PS composite score comprehensive of both verbal and visuospatial components and including performance on the PASAT 2", the PASAT 3", the letter comparison and the pattern comparison tests. No associations were reported for the composite score with any of the 6 resting-state networks investigated: default-mode (DMN), executive control, left and right fronto-parietal, cerebellar, and sensorimotor networks.

3.3. Combination of structural and functional connectivity

Papers that combined DTI and resting-state analysis were characterised by greater homogeneity in sample composition: four out of five were carried out on RRMS while only one on a mixed sample of PPMS and SPMS [62]. Clinical information was in general extensively reported, apart from the presence of depression (Table 4). Moreover, all of the studies used the PASAT 3" as test of PS functionality apart from one which investigated also the PASAT 2" [63]. Most studies used statistical correction to account for multiple comparisons, namely Bonferroni and family wise error corrections. Apart from one [34], all studies included covariates of no interest in statistical models, especially age and sex.

Compared to DTI studies, those that investigated both structural and functional connectivity, showed significantly higher quality with two out of five reaching the maximum quality score in our criteria [35,63]. However, the hypotheses underlying the aims of the studies were not always overtly reported in these papers [34,62,64].

In RRMS DTI findings confirmed those from studies focussing exclusively on this technique, showing lower fractional anisotropy and higher mean, radial, and axial diffusivity globally [63] and in the corpus callosum, the inferior and superior longitudinal fasciculi [64], thalamic tracts [35], and tracts connecting cortical areas of the DMN [34] compared to controls. Moreover, in SPMS more severe alterations of diffusivity indices were seen in the corpus callosum and the cingulum [62].

Widespread correlations between scores on the PASAT 3” and fractional anisotropy mainly centred on the corpus callosum were found in one study that used tract-based spatial statistics analysis [64]. Furthermore, several regions of interest were investigated and were found to be associated with PS performance: the corpus callosum and the cingulum, but not the corticospinal tract and the optic radiations [62]; tracts connecting the posterior cingulate and the precuneus with the right inferior parietal lobule [34]; and the anterior thalamic radiations [35]. One further study reported no correlations between the two PASAT versions analysed (2” and 3”) and global fractional anisotropy and mean diffusivity [63].

Results of studies of functional connectivity in RRMS were more variable when compared to healthy controls: thalamic connectivity was increased with dorsal and lateral frontal areas, but decreased with medial frontal, medial temporal and occipito-parietal cortices [35,63]; increased connectivity was found between various pairs of areas part of the DMN [34]; and finally decreases in functional connectivity between the left fronto-parietal network and the executive control network were found [64].

When functional connectivity was found to correlate with measures of PS, PASAT 3” score was positively associated with connectivity of the left medial prefrontal cortex and the anterior cingulate [62] and negatively with the posterior DMN on the left side [34], the ECN and the medial VN [64], and between the thalamus and distributed cortical and subcortical areas in both hemispheres [63]. Zhou et al. [35], instead, found no correlation between thalamic connectivity and performance on the PASAT 3”.

Reductions in functional connectivity were also reported in the progressive forms of MS, with slightly different patterns across phenotypes: in the medial prefrontal cortex and the precentral gyrus for SPMS; in the anterior cingulate cortex and the precentral gyrus in PPMS [62].

Finally, no correlations were observed between measures of structural and functional connectivity by studies that focused on the thalamus [35,63]. Mean and axial diffusivity in tracts connecting the anterior and posterior portions of the DMN were, however, found to be correlated with their functional connectivity [34], and fractional anisotropy in the corpus callosum and the cingulum correlated with functional connectivity of the anterior DMN [62].

Table 4. Characteristics of studies on both structural and functional connectivity

Study	Sample	Age (years)*	Duration (years)*	EDSS*	PS measure	Covariates	Analysis	Results about correlations
Rocca et al., 2010 **[62]**	75 MS: 33 SPMS 24 PPMS 24 HC	46.3 (24-65)† 47.9 (29-64)† 47.4 (26-65)†	15.5 (4-32)† 12.7 (3-39)†	6 (4-9)‡ 6 (3-8)‡	PASAT 3”	DTI: none RS: age, head motion	DTI-ROIs: CC, CST, OR, cingulum RS-ROI: DMN	PASAT 3” positively correlated with mean FA and MD in the CC and the cingulum globally; and positively correlated with RS activity of the ACC and of the left medial PFC
Tona et al., 2014 **[63]**	48 RRMS 24 HC	36.7 (8.1) 31.1 (6.5)	7.4 (6.1)	2 (1-4.5)‡	PASAT 2” PASAT 3”	Both: age, thalamic volume	DTI: whole brain RS-ROI: thalamus	PASAT 2” and 3” not correlated with DTI measures; PASAT 2” and 3” negatively correlated with FC between thalamus and several areas in both hemispheres
Zhou et al., 2014 **[34]**	24 RRMS 24 HC	39.5 (20-56)† 39.6 (21-56)†	3 (1-16)†	1.6 (1-2.5)‡	PASAT 3”	None	DTI-ROIs: tracts linking DMN areas RS-ROI: DMN	PASAT 3” positively correlated with FA in WM tract connecting the PCC/precuneus and the right IPL; and negatively correlated with increased FC between PCC/precuneus and left mTL
Sbardella et al., 2015 **[64]**	30 RRMS 24 HC	35 (8) 32 (6.1)	10.1 (6.2)	2.5 (0-4)‡	PASAT 3”	DTI: age, sex, PD-LV RS: age, sex, NGMV	DTI: TBSS RS-ROIs: 11 networks	PASAT 3” correlated positively with FA and negatively with AD, MD and RD in widespread bilateral WM tracts; and negatively correlated with FC of the ECN and of the medial VN bilaterally
Zhou et al., 2016 **[35]**	20 RRMS 20 HC	39.3 (20-57)† 38.1 (22-51)†	2 (1-3)†	1.6 (0-2.5)†	PASAT 3”	Both: age, sex, thalamic fraction	DTI-ROIs: thalamic tracts RS-ROIs: thalamus and 7 linked areas	PASAT 3” negatively correlated with mean AD in the whole WM tracts between thalamus and PFC; PASAT 3” not correlated with thalamic FC

ACC: anterior cingulate cortex, CC: corpus callosum, CST: corticospinal tract, DMN: default mode network, DTI: diffusion tensor imaging, ECN: executive control network, FC: functional connectivity, IPL: inferior parietal lobule, ISD: individual standard deviation, mTL: medial temporal lobe, NF: not fatigued, NGMV: normalised grey matter volume, OR: optic radiations, PCC: posterior cingulate cortex, PD-LV: lesion volume on proton density images, ROI: region of interest, RRMS: relapsing-remitting multiple sclerosis, RS: resting state, RT: reaction time, SFG: superior frontal gyrus, VN: visual network, WF: with fatigue

* Mean (Standard deviation)
† Mean (Range)
‡ Median (Range)

4. Conclusions and future directions

The aim of this review was to summarise current knowledge on how brain connectivity measures in MS are associated with PS function, a cognitive domain known to be particularly affected, and to provide insight for future lines of research.

The published literature shows contrasting results on correlations between PS function and measures of functional and structural connectivity. DTI studies have highlighted mainly vague and variable findings. Indeed, when voxel-wise analyses were carried out, multiple and widespread clusters of WM correlated with PS tasks [29,39,41,55,57,58] and the same was observed in the investigation of more specific regions of interest across a range of tests [42,43,50,51,54]. Lack of correlation with brain connectivity measures was noted more often for the PASAT (especially the 3" version) than the SDMT and various explanations may account for these differences. Firstly, the sensory modality used to present stimuli differs between the two tests: auditory for the PASAT and visual for the SDMT. The latter, in fact, has been reported to be more susceptible to impairment in MS than the former and may better evaluate PS deficits associated with this disease [65]. Secondly, the way stimuli are presented during test performance differs across tests: for the PASAT stimuli are presented one at a time in sequence, while all the stimuli are presented simultaneously on the same page for the SDMT, thus increasing the demands posed on inhibition of processing of possible distractors. For the PASAT, it has also been suggested that patients may put in place different solving strategies when facing different versions of the PASAT. In fact, Snyder et al. [66] reported that patients tend not to perform the task continuously but to skip every third item, thus reducing considerably the difficulty of the test and achieving a higher, though less reliable, score. Finally, we cannot ignore that the two tests, although both used as PS measures, require the engagement of different cognitive domains: verbal auditory working memory for the PASAT and visual attention for the SDMT. These cognitive functions are long known to rely on activity of different brain areas of both hemispheres [67], suggesting these tasks may assess different aspects of the PS function.

Indeed, partially different WM tracts were observed to be related to the tests reviewed. Performance on the PASAT was more associated to the level of microstructural integrity of the left cingulum, the superior longitudinal fasciculus (especially left-lateralised), and the inferior longitudinal fasciculus. The SDMT, instead, seems to be more associated to DTI measures in bilateral tracts: the fornix, the cingulum and the posterior thalamic radiations. However, the corpus callosum emerged as the WM

tract that most consistently correlated with PS performance of people with MS across cognitive tasks. This suggests the importance of multiple WM tracts to support cognitive PS performance across cognitive domains through fast integration of information processed in distributed brain networks. Despite the variability of results, DTI indices seem to be more consistently correlated with different PS performance than measures of lesion load and parenchymal atrophy. This may result from the fact that microstructural WM damage can spread across fibre tracts [68], and can precede the detection of new macrostructural lesions [69]. Hence, diffusion indices may be more sensitive in detecting subtle MS pathology leading to decline in PS function than conventional MRI. In fact, apart from commissural fibres (i.e. the corpus callosum) associative WM tracts appear to be more critically involved in PS performance, namely the superior and inferior longitudinal fasciculi and the cingulum. Nevertheless, given the variability in PS tasks used, differential WM involvement may have been detected according to the specific measures used.

In contrast, higher quality and more consistent results were observed in RS-fMRI studies. Functional neuroplasticity seems to be the underlying mechanism supporting cognitive changes, or stability, in the early phases of MS. In fact both people with clinically isolated syndrome and RRMS showed functional connectivity changes, both increases [34,35,63] and decreases [35,59,60,63,64], within various brain networks. Furthermore, PS performance correlated with functional connectivity alterations in frontal areas, such as the prefrontal and anterior cingulate cortices, and fronto-thalamic connections [31,35,60,62,64]. It is also worth noting that, in contrast to DTI studies, almost all those studies exploring functional connectivity used exclusively the PASAT to measure PS abilities.

Even though a relationship between macrostructural damage and resting-state functional changes in MS appears likely [70], current findings are not consistent. In fact, while some studies observed correlations between total lesion volume and changes of resting-state activity [35] others reported no correlation [62,64]. The same discrepancy has been observed about the association between structural and functional connectivity measures, where significant correlations were found only in a small number of studies [34,62]. Indeed, the relationship between functional and structural brain changes may not be that straightforward in consideration of the fact that if structural connectivity between two areas predicts functional connectivity, the reverse is not necessarily the case, since functional connectivity can also depend on indirect connections to and from other brain areas [71].

Current knowledge of how MS-related damage to both structural and functional connectivity affects PS function is incomplete and preliminary. This may be due to methodological shortcomings detected in the reviewed articles. Firstly, most studies, especially those on structural connectivity, were carried out on samples of mixed MS phenotypes. Such lack of differentiation may confound results, particularly since the neuropathology in progressive forms of MS is increasingly recognised to be mainly characterised more by neurodegenerative rather than inflammatory processes [72]. Secondly, to date many studies have been carried out using a more explorative approach, often without a clearly defined hypothesis to test, and have been based on a cross-sectional design that does not allow for the assessment of PS decline over time. Finally, a lack of theoretical background on PS decline in MS has emerged from the published literature. The majority of the studies focused mainly on the most common tests of PS that are intrinsically related to various cognitive domains (i.e. working memory for the PASAT and visuospatial attention for the SDMT), neglecting alternative strategies of investigation. These could include better characterisation of the neural correlates of PS deficits in MS considering sensory, cognitive, and motor contributions [9] or clarifying any possible influence of PS decline on other cognitive domains when assessing correlations with MRI measures [41].

PS performance has been repeatedly found to be impaired in people with MS and to correlate with both structural and functional brain reorganisation, in particular degeneration of the corpus callosum [37-39,41,46,47,49,52,56,57,62] and altered activity in frontal areas [31,60,62,64]. Nevertheless, the dynamic properties and topography of neural breakdown in MS have yet to be clarified. Recent meta-analyses have been published with the aim of advancing our understanding of brain regions mostly affected by MS. Lansley et al. [73] showed that GM appears to degenerate especially in the thalamus, a crucial hub for information distribution across the brain, the basal ganglia, precentral and postcentral gyri, and the cingulate cortex, involved in complex cognitive functions. Furthermore, Welton at al. [26] highlighted how WM microstructural degeneration could be functionally related: physical disability was found to be mainly related to the posterior corpus callosum and right inferior fronto-occipital fasciculus, while cognitive decline was mainly linked to the anterior part of the corpus callosum, the thalamus, and the fornix.

The published literature suggests that connectivity of the frontal cortices and between hemispheres is involved in PS function in MS. Interestingly, the cognitive efficiency theory [74] postulates that activity of the prefrontal cortex plays a pivotal role in PS performance as do dynamic interactions with parietal

cortices [75-77]. However, caution is needed when drawing conclusions based on current published evidence in light of the limitations we have identified. In fact, only a review by Lopes Costa et al. [9] has extensively explored the issue regarding a thorough definition of PS. Further theoretical discussion on MS-related cognitive impairment may aid the stimulation of a more hypothesis-driven approach to plan future investigations.

This review has some limitations: studies carried out on mixed MS phenotypes were included and all articles written not in English, though very few, were excluded. Possible selection bias was minimised during the review process by carrying out a systematic search of the literature on the topic without setting strict limitations (e.g. narrow time windows). All papers investigating at least a measure of PS were included, though the possibility of having missed eligible records cannot be completely ruled out. No specific issues regarding publication bias were detected through quality assessment, since different studies also reported negative results and most studies discussed their own limitations.

In conclusion, whilst reviewed studies have shown significant promise for the use of resting-state functional MRI and DTI to explore the neural substrates underpinning of PS in MS, results to date have not been consistent, and future investigations may benefit from considering the limitations identified in this review. Firstly, more detailed analysis of concepts related to PS function should be brought about in order to provide better theoretical frameworks to the neuroscientific investigation of this domain and its decline due to MS [9]. Secondly, the differential associations between different measures of PS ability, which may potentially capture different cognitive aspects of this function, and their neural correlates need further characterisation. Thirdly, the use of a longitudinal design, that so far has been largely neglected, is needed to clarify the interplay between neural and cognitive changes over time and potential maladaptive plasticity in MS. Indeed, Loitfelder et al. [78] observed that higher activity in the left inferior parietal lobule at 1-year follow-up was negatively correlated with SDMT performance in RRMS. Finally, considering the higher scientific quality observed in studies combining different connectivity measures we argue that the use of multimodal imaging with a focus on network and graph theory analyses [33,61] may prove to be particularly helpful in tracking PS decline in MS. Combined use of different MRI techniques might allow a more comprehensive approach to mapping connectivity that may help unravel the complexity that characterises MS symptoms. Furthermore, the integration of multimodal MRI and targeted neuropsychological assessment may provide more detailed outcome measures also in clinical trials, both for

pharmacological and non-pharmacological interventions, and highlight beneficial treatment effects that may go otherwise undetected.

Conflicts of interest: none.

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Appendix A. Search strategy

Table A.1 | Strings with keywords used in the literature search

"multiple sclerosis"	AND	**DTI**	AND	**"information processing"**
"multiple sclerosis"	AND	**DTI**	AND	**"processing speed"**
"multiple sclerosis"	AND	**DTI**	AND	**"speed of processing"**
"multiple sclerosis"	AND	**DTI**	AND	**PASAT**
"multiple sclerosis"	AND	**DTI**	AND	**SDMT**
"multiple sclerosis"	AND	**"resting state"**	AND	**"information processing"**
"multiple sclerosis"	AND	**"resting state"**	AND	**"processing speed"**
"multiple sclerosis"	AND	**"resting state"**	AND	**"speed of processing"**
"multiple sclerosis"	AND	**"resting state"**	AND	**PASAT**
"multiple sclerosis"	AND	**"resting state"**	AND	**SDMT**
"multiple sclerosis"	AND	**"functional connectivity"**		
"multiple sclerosis"	AND	**"structural connectivity"**		

Appendix B.

Table B.1 | Quality assessment criteria

Area	Question	Values
Methodology	**1. Were a priori hypotheses clearly stated?**	no = 0; yes = 1
	2. How large was the sample size?	< 30 = 0; ≥ 30 = 1
Clinical characteristics	**3. What MS phenotypes were included?**	not defined = 0; mixed = 1; one type only or distinct groups = 2
	4. Was information on history of comorbidities reported?	no = 0; yes = 1
	5. Was information on pharmacological treatments reported?	no = 0; yes = 1
	6. If RRMS was included, was information on relapses reported?	no = 0; yes = 1
MRI parameters	**7. How strong was the MRI field used?**	1.5 T = 0; ≥ 3 T = 1
	8. How many diffusion-weighted directions, for DTI, or slices, for resting-state fMRI, were acquired?	< 30 or missing = 0; ≥ 30 = 1
Statistical analysis	**9. Was the imaging analysis coherent with the hypothesis?**	no = 0; yes = 1
	10. Was correction for multiple comparisons used?	no = 0; yes = 1
	11. Were covariates of no interest included in the analysis or, if not, was their exclusion motivated?	no = 0; yes = 1
Results	**12. Were limitations of the studies clearly stated?**	no = 0; yes = 1

Table B.2 | Quality assessment of DTI studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	TOT
Lin et al. 2008	0	1	2	1	1	0	0	0	1	0	0	0	**6**
Roca et al., 2008	0	0	2	1	1	1	0	0	1	0	0	0	**6**
Bonzano et al., 2009	0	1	2	1	1	1	0	0	1	0	0	0	**7**
Dineen et al., 2009	0	1	2	1	1	1	1	0	1	1	1	1	**11**
Mesaros et al., 2009	0	1	1	1	1	1	0	0	1	1	1	1	**9**
Roosendaal et al., 2009	0	1	1	0	0	0	0	0	1	0	1	0	**4**
Warlop et al., 2009	1	0	0	0	0	0	1	0	1	0	0	1	**4**
Ozturk et al., 2010	1	1	1	0	0	1	1	1	1	1	0	1	**9**
Van Hecke et al., 2010	0	1	1	0	0	1	0	1	1	1	0	1	**7**
Rimkus et al., 2011	0	1	2	0	1	1	1	1	1	0	0	0	**8**
Llufriu et al., 2012	1	1	2	0	1	1	0	1	1	0	0	1	**10**
Yu et al., 2012	0	1	2	0	0	0	1	0	1	1	1	1	**8**
Benedict et al., 2013	0	1	1	1	1	1	1	0	1	0	1	1	**9**
Bester et al., 2013	1	1	1	1	1	1	1	0	1	1	1	1	**11**
Bozzali et al., 2013	0	1	2	0	1	1	1	1	1	1	1	1	**11**
Genova et al., 2013	1	1	1	0	0	0	1	0	1	1	1	1	**8**
Mazerolle et al., 2013	1	1	2	1	1	1	0	0	1	1	1	1	**11**
Sbardella et al., 2013	0	1	2	1	1	1	1	1	1	1	1	1	**12**
Koenig et al., 2014	0	1	1	0	0	0	1	1	1	0	0	1	**6**
Kern et al., 2015	1	1	2	1	1	1	1	1	1	0	0	1	**11**
Koenig et al., 2015	0	1	1	0	0	0	1	1	1	1	0	1	**7**
Meijer et al., 2016	1	1	2	1	0	1	1	0	1	1	1	1	**11**
Moroso et al., 2017	1	1	2	1	1	1	1	0	1	0	0	1	**10**

Table B.3 | Quality assessment of RS-fMRI studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	TOT
Janssen et al., 2013	1	1	2	1	1	0	1	1	1	1	0	1	**11**
Gamboa et al., 2014	1	1	1	0	0	0	1	1	1	0	0	0	**6**
Wojtowicz et al. 2014	0	1	2	1	1	1	0	0	1	0	1	1	**9**
Pravatà et al., 2016	1	1	2	1	1	1	1	1	1	0	1	1	**12**

Table B.4 | Quality assessment of studies combining DTI and RS-fMRI

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	TOT
Rocca et al., 2010	0	1	2	0	1	1	1	1	1	0	1	1	**10**
Tona et al., 2014	1	1	2	1	1	1	1	1	1	1	1	1	**13**
Zhou et al., 2014	0	1	2	0	1	1	1	1	1	1	0	1	**10**
Sbardella et al., 2015	0	1	2	1	1	1	1	1	1	1	1	1	**12**
Zhou et al., 2016	1	1	2	1	1	1	1	1	1	1	1	1	**13**