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Neurite Orientation Dispersion and Density Imaging in Multiple Sclerosis: A Systematic Review

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Diffusion-weighted imaging has been applied to investigate alterations in multiple sclerosis (MS). In the last years, advanced diffusion models were used to identify subtle changes and early lesions in MS. Among these models, neurite orientation dispersion and density imaging (NODDI) is an emerging approach, quantifying specific neurite morphology in both grey (GM) and white matter (WM) tissue and increasing the specificity of diffusion imaging. In this systematic review, we summarized the NODDI findings in MS. A search was conducted on PubMed, Scopus, and Embase, which yielded a total number of 24 eligible studies. Compared to healthy tissue, these studies identified consistent alterations in NODDI metrics involving WM (neurite density index), and GM lesions (neurite density index), or normal-appearing WM tissue (isotropic volume fraction and neurite density index). Despite some limitations, we pointed out the potential of NODDI in MS to unravel microstructural alterations. These results might pave the way to a deeper understanding of the pathophysiological mechanism of MS.
Evidence Level: 2.
Technical Efficacy: Stage 3.

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Multiple sclerosis (MS) is a disabling neurological disease characterized by inflammation, demyelination, and axonal loss of the central nervous system.[1] This chronic lifelong condition affecting the brain and spinal cord occurs when the immune system attacks nerve fibers and myelin sheathing causing a wide range of deficits. These symptoms include loss of vision, loss of arm or leg power, or a rising sense of numbness in the legs.[2] There is no cure for MS so far. A deeper understanding of the pathophysiological mechanisms might help to shed new lights aimed at driving future treatments speeding recovery from attacks, modifying the course of the disease, or managing symptoms.

To date, several approaches have been applied to investigate neuropathological mechanisms. While conventional structural MRI (sMRI, eg FLAIR or T2-weighted images) remains a valuable tool in the identification of MS through a lifespan continuum, a major drawback is its low specificity in the accurate detection of potential microscopic pathological alterations.[3] MS abnormalities in white matter (WM) and grey matter (GM) tissues and in the peri-lesion areas that appear normal on conventional sMRI are observed in MS disease.[4] Similarly, tissue damage to outer macroscopic lesions not detectable by conventional sMRI can contribute to clinical disability,[5] suggesting that identifying the whole spectrum of MS lesions and alterations within nonlesion areas represents a critical step for a deeper understanding of the pathophysiological mechanisms.

Diffusion-weighted imaging (dMRI) is an advanced MRI approach aimed at assessing microstructural changes. This technique is not an alternative to sMRI, but it can provide additional information to better understand the pathophysiology of

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the disease. DWI is based on brain water diffusion metrics, allowing to the evaluation of the molecular function and microarchitecture of the brain.[6] The most commonly used model for estimating dMRI-based metrics representing the microstructural tissue properties is diffusion tensor imaging (DTI), which provides information on fiber organization, axonal directional coherence, and tract integrity.[7] DTI allows to measure the transitional motion of water deriving, information about the anisotropy of different brain tissues, which can inform about brain abnormalities for several neurological disorders.[8] Four different DTI outcomes, including fractional anisotropy (FA) and mean/axial/radial diffusivity (MD/AD/RD), are commonly used to quantify the shape of the tensors in each brain voxel. FA is sensitive to axonal integrity, although multiple factors can underlie FA alterations (i.e. cell death, gliosis, demyelination, increase in extracellular or intracellular liquid content, inflammation, and axonal loss). Therefore, FA might not be a specific parameter to define the type of changes.[9] Another metric usually investigated jointly with FA is MD. High MD is indicative of increased extracellular spaces because of shrinkage or degeneration of axons and dendritic fibers.[10] Although DTI is the most common model applied in the study of brain WM diseases and is relatively easy to implement, this approach can be affected by several confounding factors, such as tissue properties, affecting the specificity of this metric for different neuropathological substrates.[11] Furthermore, since GM diffusion is nearly isotropic, DTI is not suitable to investigate GM abnormalities.[12]

Neurite orientation dispersion and density imaging (NODDI) is an advanced diffusion model applied to quantify specific neurite morphology in both GM and WM.[13] See Fig. 1 for a vis-à-vis comparison between NODDI and DTI model. NODDI is based on a three-compartment tissue model, which includes an intraaxonal compartment with restricted anisotropic non-Gaussian diffusion (neurite density index [NDI]), an extra-neurite compartment with constrained anisotropic Gaussian diffusion (orientation dispersion index [ODI]), and a water compartment with free Gaussian and isotropic diffusion (isotropic volume fraction [ISOVF]) (Fig. 2).[14] Recent findings have shown high NODDI sensitivity in detecting changes in normal-appearing WM (NAWM). NAWM refers to the normal yet diseased tissue around the WM hyperintensities (WMH) on conventional MR images. Normal-appearing GM (NAGM) possesses a similar definition as being a part of normal-looking and diseased GM without focal lesions.[15] Similarly, NODDI showed greater specificity in detecting microstructural features in MS patients compared to DTI.[16] A number of studies have compared NODDI metrics and DTI-derived FA regarding their sensitivity in detecting microstructural integrity in MS. They reported that NODDI values are more sensitive to MS changes and can detect abnormalities in brain regions exhibiting normal FA distributions.[16,17] Despite these promising results, it is still unclear whether NODDI represents a suitable technique to detect consistent MS alterations.[18] Recently, Alotaibi et al performed a systematic review of NODDI findings in MS, including only seven studies.[13] In the last years, several new studies were performed, as NODDI is increasingly becoming the standard model for DWI images. Moreover, in their analysis only WM findings were reported, while information from GM lesions and normal-appearing GM could shed new light on the pathophysiological mechanisms of MS. Due to the heterogeneity results of previous studies, we conducted a comprehensive and up-to-date systematic review of NODDI studies on this neurological disease, including studies investigating NODDI outcomes in both GM and WM lesions and normal-appearing tissues.

Methods and Materials

The present systematic review study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) consensus statement (CRD42022335396).[19]

Search Strategy and Eligibility Criteria

A comprehensive literature search was conducted using three online databases, PubMed, Embase, and Scopus, in November 2022. The following search keywords were used: "NODDI" or "Neurite Density" or "Orientation Dispersion" or "neurite orientation dispersion and density imaging" and "Multiple Sclerosis" or "Sclerosis, Multiple" or "Sclerosis, Disseminated" or "Disseminated Sclerosis" or "MS (Multiple Sclerosis)" or "Multiple Sclerosis, Acute Fulminating." Additional records were identified in the reference list of the included studies. We included observational studies investigating GM and WM changes in NODDI measurements of MS patients compared with healthy controls (HC): 1) cross-sectional study (collect information for each single individual at a single point in time); 2) case–control investigations (involve determining risk factors for an outcome of interest); and 3) cohort studies (compare outcomes among participant groups based on their exposure to a risk factor).[20] We excluded studies without reporting contrast analysis between MS and controls. Eligibility criteria were not restricted based on nationality, publication time, age, sex, or disease stage. Review articles, interventional investigations, case series, case reports, in vitro and animal studies were excluded.

Study Selection

Two independent reviewers (H.S. and F.N.) performed the screening process in two steps. First, the title and abstracts were reviewed, and irrelevant studies were excluded. Then, for final selection, the full text of the remained articles was carefully screened to check whether they met our eligibility criteria. Any disagreements were resolved by consulting with the third investigator (M.A.). The following data were extracted from the studies included in the review: study groups, sample size, demographic data, Expanded Disability Status Scale (EDSS), disease

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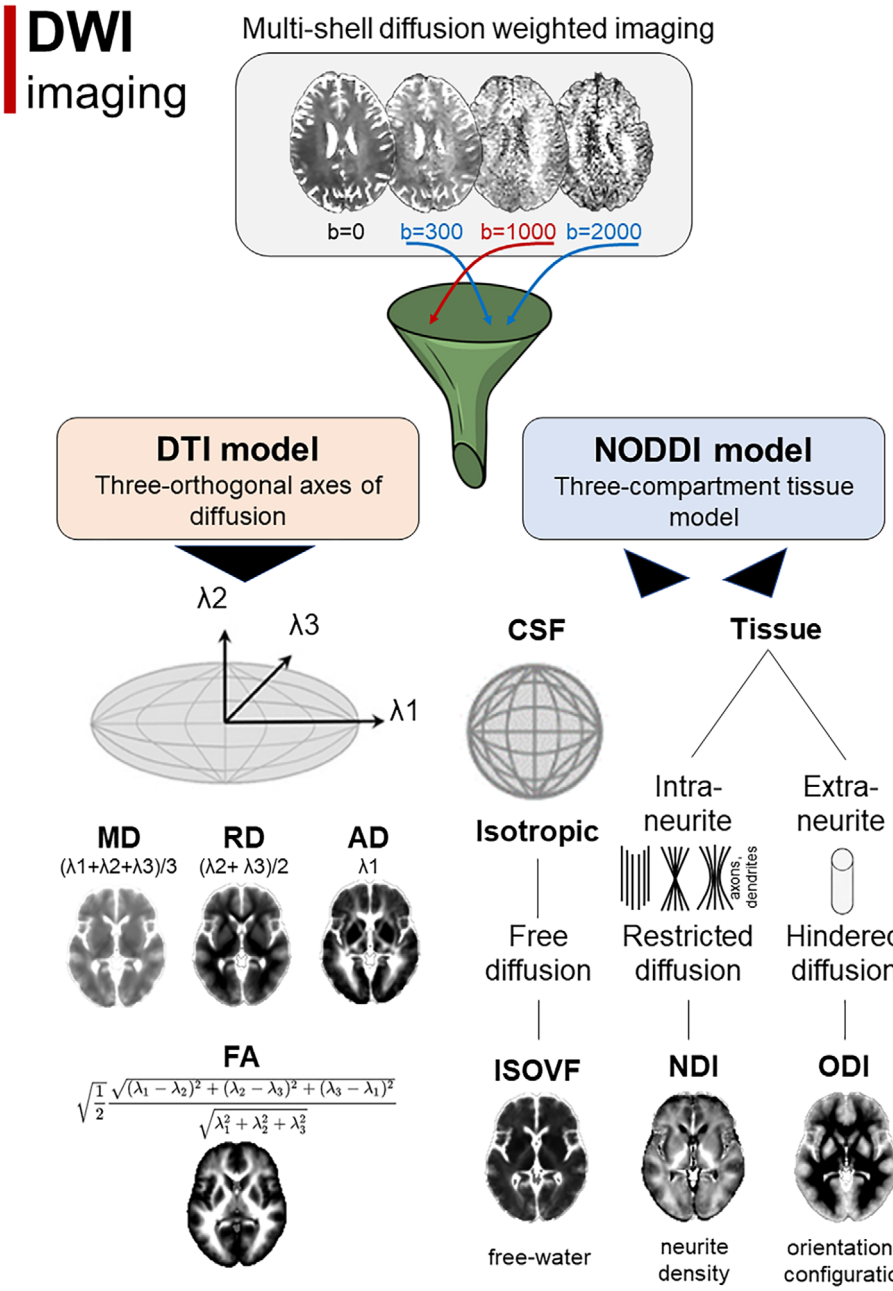

FIGURE 1: Diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI) can be computed from multi-shell diffusion imaging (for DTI specific b-values can be selected from the full acquisition). While the DTI model is based on three orthogonal axes of diffusion, NODDI is a three-compartment tissue model, which can provide information about the cellular environment. NODDI and DTI maps were computed from DWI data of a large dataset of the Human Connectome Project ($n = 1065$). Maps were nonlinearly normalized to the MNI template and averaged for comparison purpose.

duration, analytical toolbox, acquisition parameters, target brain regions, NODDI indices, analysis method, and study results.

Quality Assessments

The quality of the included studies was assessed using the Newcastle-Ottawa scale (NOS). The quality of case–control and cohort studies was measured for multiple aspects, including selection, comparability, exposure, and outcome.[21] A total rate equal or less than four highlights a low-quality score; a range from four to six expresses an intermediate quality score; a score from seven to nine represents an high-quality score.[22]

Results

Included Studies

The systematic search in the three databases retrieved a total number of 241 studies. After the removal of 120 duplicates, we screened the remaining 121 studies through title and abstract. After the exclusion of unrelated studies and checking

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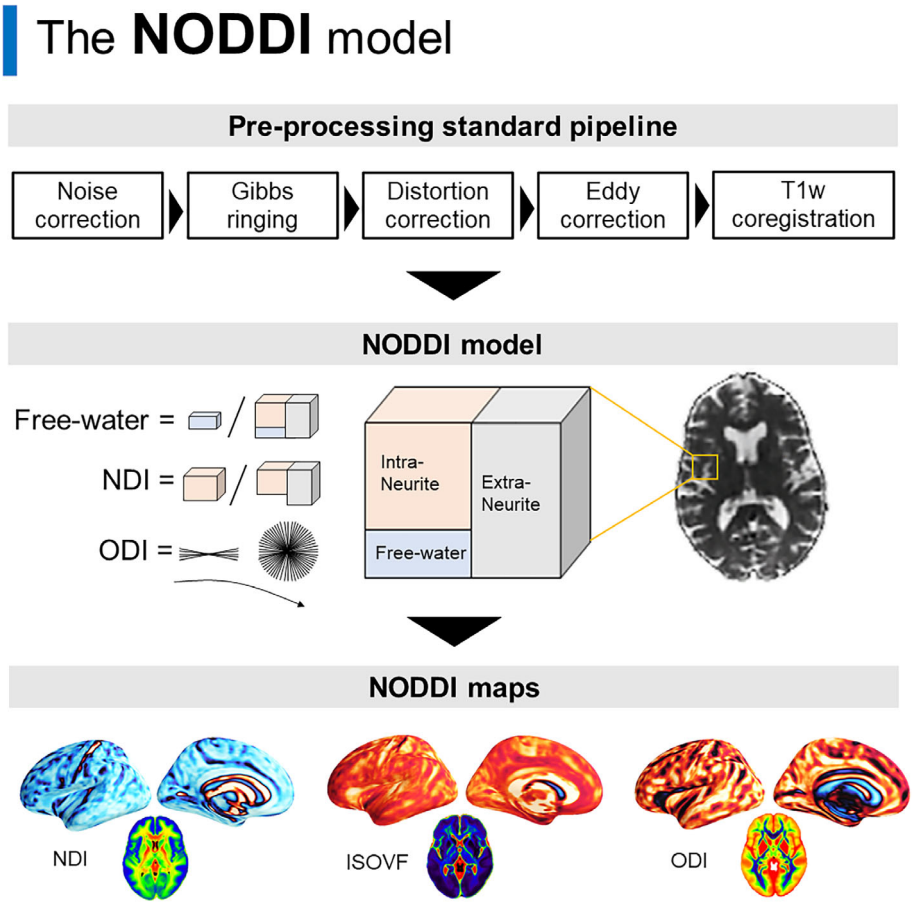

FIGRUE 2: A schematic representation of NODDI computation and the principle of the model. NODDI maps were computed from the Human Connectome Project dataset ($n = 1065$) and registered to the inflated fsaverage space (surface) and the MNI152 volume atlas.

the full texts, 24 studies were found to be eligible for our systematic review. Figure 3 shows the PRISMA diagram and exclusion criteria. The 24 articles included in the final review encompassed 1155 MS patients (sample range 5–172) and 695 HC (sample range 5–76), as shown in Table 1. Of all the MS cases, 817 were patients with relapsing–remitting MS (RRMS), 245 patients had a diagnosis of primary progressive MS (PPMS), 18 were patients with secondary progressive MS (SPMS), 7 patients were clinically-isolated syndrome (CIS), while for 68 cases the clinical phenotype was not reported. A total of 742 female patients were included, while for 39 patients' gender was not specified.

The publication year of the studies ranged from 2017 to 2022. As expected, these studies applied a different range of analysis on the NODDI metrics. These approaches included grey matter-based spatial statistics (GBSS),[23] region-of-interest (ROI),[16,18,23,25,26,28,30–33,35,36,38–40,43,44] cortical surface mapping,[24,30] whole-brain analysis,[27] tract-based spatial statistics (TBSS),[28,29,31,33,34,37] and voxel-based analysis (VBA).[32,41,42] A more homogeneity was reported for the toolboxes used for this analysis. Eighteen of the included studies applied NODDI matlab toolbox (https://www.nitrc.org/projects/noddi_toolbox), three studies used accelerated microstructure imaging via convex optimization (https://github.com/daducci/AMICO), two studies used the spherical mean technique,[45] while microstructure diffusion toolbox was used in a single study (https://github.com/robbert-harms/MDT). Data features of the included studies are shown in Table 1.

As shown in Table 2, 15 studies assessed NODDI metrics within MS lesions,[16,18,24,25,28,30–34,37–40,43] although the approaches implemented by the authors were different. The remaining studies focused on normal-appearing or specific tissues of the participants. Overall, the included studies can be conceptualized into three main groups: 1) between-group studies comparing lesions' NODDI outcomes with NODDI normal brain tissues computed from HC[16,24,25,28,31–33,35,38,40,43]; 2) within-patient studies comparing MS lesions' NODDI metrics with normal-appearing tissues from patients themselves[16,18,24,25,30,35,38,39]; 3) between-group studies comparing between MS whole NAWM and normal-appearing GM (NAGM) and normal tissues of HC.[16,18,24–26,28,30–32,35–38,40,41]

Quality Assessment of the Included Studies

The quality of the included studies is shown in Table S1 Supplementary Material. Cohort studies were assessed based on case selection, comparability, and outcome, yielding a total score of 6–9. Case selection, comparability, and exposure of

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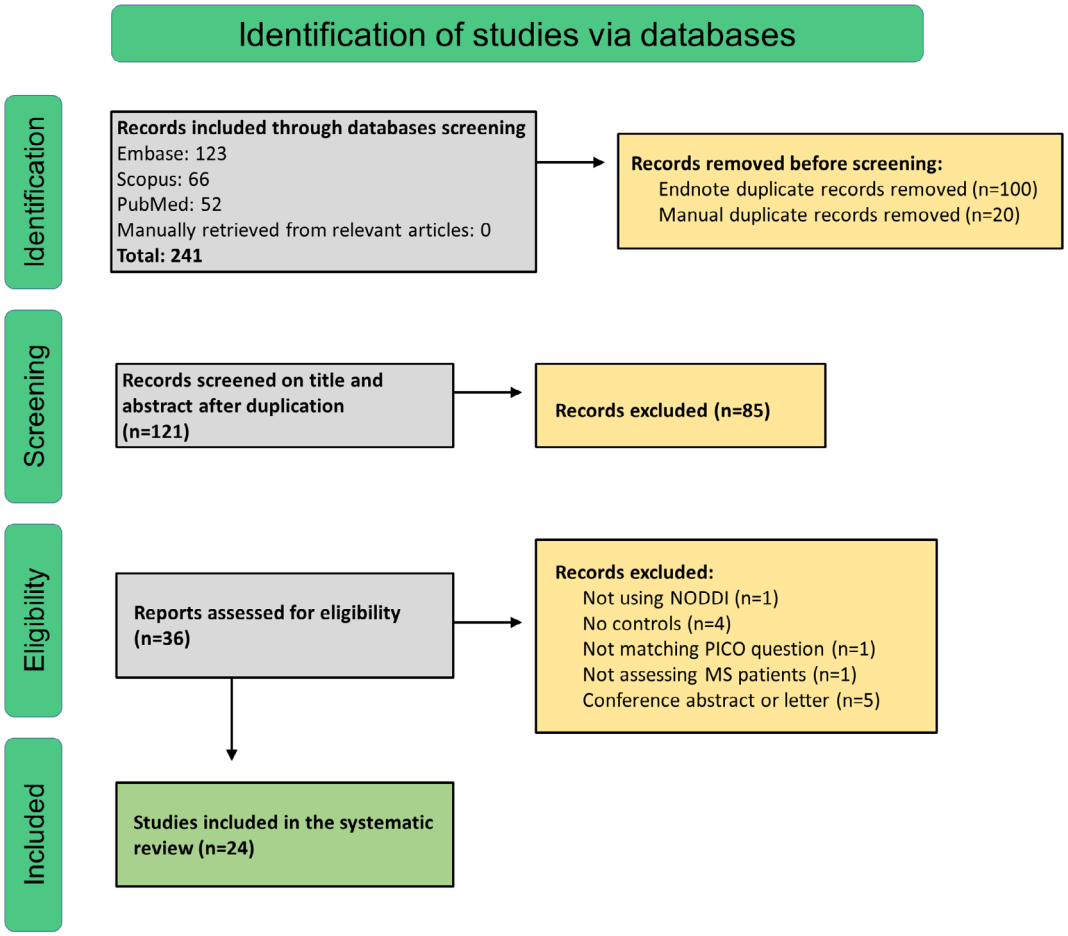

FIGURE 3: Study selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

case–control studies scores ranged from 5 to 7. Among the 24 studies, 18 studies had high quality (7–9 NOS scores), six studies had intermediate quality (4–6 NOS scores), and none were low-quality studies (Table S1). Participants were age-matched in four studies,[24,28,37,39] sex-matched in one study.[36] Meanwhile, 15 studies controlled for both age and gender.[16,18,23,26,27,29–31,33–35,40–43]

WM Lesions and NAWM

WM lesions refer to those lesions primarily involving WM regions according to sMRI. These lesions were assessed in the majority of the studies retrieved compared to GM lesions. Decreased NDI was the most consistent NODDI feature in WM lesions. Specifically, NDI showed systematic reduction within WM lesions compared to NAWM[16,18,30,38,39] and normal WM (NWM, that is WM from healthy individuals).[16,25,28,31–33,38–40,43] Studies also reported reduced NDI values in MS NAWM compared to WM in HC. These findings suggest an overall NDI reduction in WM tissues and lesions in MS,[16,26,28,30,32,36,37,40,41] although two independent studies reported null NDI effects between MS and control cohorts.[18,31]

Conversely, ODI values showed an unclear pattern. Four studies highlighted reduced ODI in WM lesions compared to NWM from HC,[16,28,31,33] while opposite findings were reported in two independent studies.[25,40] One study even indicated comparable ODI values in MS WM lesions and NWM of controls.[43] Similar incongruent results were observed when investigating ODI in WM lesions compared to NAWM.[16,18,30] Moreover, ODI showed heterogeneity when comparing the NAWM of patients and the NWM of HC. Two studies here included reported lower ODI in NAWM[28,40]; four independent findings reported higher ODI,[16,25,31,37] while three studies showed similar ODI measures between MS NAWM and controls.[18,26,30] Overall, these results suggest a heterogeneous pattern of ODI which might be sensible to different brain tissue properties.

Regarding ISOVF, three studies reported higher values in WM lesions than NAWM of patients[18] and NWM of healthy people[16,33]; however, two independent studies reported unchanged ISOVF values in lesions.[25,30] The results of the NAWM and NWM comparison were more homogenous, as most studies reported no difference between their ISOVF metrics[16,18,25,30,37] and only one study demonstrated higher ISOVF in patients' NAWM.[31]

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TABLE 1. Main Characteristics of the Studies Included

Author/Year	Study Design	Study Groups	Sample Size	F/M Ratio	Age (Mean ± SD)	EDSS	Disease Duration in Years (Mean ± SD)	Toolbox	Acquisition Parameters
Andica et al, 2022[23]	Case–control	RRMS HC	30 19	24/6 13/6	51.43 ± 8.02 51.47 ± 9.25	Median: 2 Range: 0–7	12.10 ± 4.76	NODDI MATLAB Toolbox	3 T directions: 30, 60 b: 1000, 2000
Barletta et al, 2021[24]	Cohort	RRMS HC	25 19	21/4 10/9	38.2 ± 8.9 35.8 ± 10.2	Median: 2 Range: 0–4	Median: 1.9 Range: 0.6–4.7	NODDI MATLAB Toolbox	3 T directions: 64, 128 b: 1000, 5000
By et al, 2017[25]	Cohort	RRMS HC	6 8	6/0 3/5	39.3 ± 6.1 29 ± 5	Mean: 2.5 SD: 2.1	7 ± 6	NODDI MATLAB Toolbox	3 T directions: 32, 64 b: 711, 2855
Chen et al, 2021[18]	Cohort	CIS RRMS SPMS HC	4 11 3 9	12/6 5/4	45.5 ± 14.6 41.7 ± 10	Median: 1.0 Range: 0–6.5	11.5 ± 10.6	NODDI MATLAB Toolbox	3 T Directions: 45 b: 1000, 2500
Collorone et al, 2020[26]	Cohort	RRMS HC	28 20	23/5 13/7	39.4 ± 6.6 36.6 ± 12.5	Median: 2.5 Range: 1–6.5	8 ± 5.6	NODDI MATLAB Toolbox	3 T directions: 8, 30, 60 b: 300, 1000, 2855
Collorone et al, 2021[27]	Cohort	CIS and MS HC	42 16	23/19 9/7	33.1 ± 1.03 33.3 ± 1.7	Median: 1.5 Range: 0–3	2.1 ± 1.2 Months	NODDI MATLAB Toolbox	3 T directions: 8, 15, 30 b: 300, 711, 2000
De Santis et al, 2019[28]	Cohort	RRMS HC	7 6	N/A	42 ± 15 42 ± 15	Median: 1 Range: 0–3	21 ± 11 months	MDT	3 T and 7 T directions: 27, 45, 106 b: 700, 2000, 750–6000
Gharaylou et al, 2021[29]	Cohort	Familial MS Sporadic MS HC	16 10 40	N/A N/A 22/18	Median: 34, Range: 19–53 Median: 30, Range: 19–40 Median: 35, Range: 19–60	Median: 2, Range: 1.5–3 Median: 1.75, Range: 0–6.5	Mean: 6.5, Range: 1–18 Mean: 7, Range: 1–12	NODDI MATLAB Toolbox	3 T directions: 30, 64 b: 700, 2000
Granberg et al, 2017[30]	Cohort	RRMS HC	26 24	21/5 17/7	39 ± 8.2 37.7 ± 10.6	Median: 1.5 Range: 0–4	2.5 ± 1.4	NODDI MATLAB Toolbox	3 T directions: 64, 128 B: 1000, 5000

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TABLE 1. Continued

Author/Year	Study Design	Study Groups	Sample Size	F/M Ratio	Age (Mean ± SD)	EDSS	Disease Duration in Years (Mean ± SD)	Toolbox	Acquisition Parameters
Hagiwara et al, 2019[31]	Case–control	RRMS HC	24 24	19/5 19/5	39.83 ± 8.25 39.50 ± 11.13	Median: 1 Range: 0–7	11.82 ± 5.99	AMICO	3 T directions: 30, 60 b: 1000, 2000
Johnson et al, 2021[32]	Case–control	RRMS HC	63 28	48/15 19/9	47 ± 7.6 35.1 ± 10.2	Median: 2 Range: 0–6.5	14.6 ± 2.4	NODDI MATLAB Toolbox	3 T directions: 8, 15, 30 b: 300, 711, 2000
Kato et al, 2022[33]	Case–control	RRMS HC	30 20	26/4 14/6	50.07 ± 7.16 51.80 ± 8.93	Mean: 1.80 SD: 1.75	11.30 ± 4.61	NODDI MATLAB Toolbox	3 T directions: 30, 60 B: 1000, 2000
Margoni et al, 2022[34]	Cohort	RRMS HC	27 26	19/8 16/10	36.2 ± 11.7 32.8 ± 11.3	Median: 1.5 IQR: 1–2	1.7 ± 1.3	NODDI MATLAB Toolbox	3 T directions: 8,32, 64 b: 300, 1000, 2000
Preziosa et al, 2022[35]	Cohort	RRMS PPMS HC	101 71 62	61/40 44/27 37/25	Median: 41.8, IQR: 31.4–46.4 Median: 50.0, IQR: 43.9–57.4 Median: 41.2, IQR: 32.8–49.5	Median: 2, IQR: 1–2.5 Median: 6, IQR: 5.5–6.5	Median: 5, IQR: 1–14.5 Median: 19, IQR: 10–25.7	NODDI MATLAB Toolbox	3 T directions: 6, 30, 60 b: 700, 1000, 2850
Preziosa et al, 2022[36]	Cohort	RRMS and PPMS HC	152 (RRMS/PPMS: 91/61) 48	95/57 27/21	44.3 ± 10.9 42.1 ± 9.9	Median: 3.5 IQR: 1.5–6	Median: 11 IQR: 2.0–22.0	NODDI MATLAB Toolbox	3 T 6, 30, and 60 directions b = 700, 1000, 2850
Radetz et al, 2021[37]	Case–control	RRMS HC	50 49	31/19 25/24	35.3 ± 11.1 31.5 ± 9.1	Median: 1 IQR: 1.25	50 ± 59 Months	AMICO	3 T directions: 30 b: 900, 1800, 2700
Rahmanzadeh et al, 2021[38]	Cohort	RRMS and PPMS HC	91 (RRMS/PPMS: 62/29) 72	56/35 43/29	46 ± 14 36 ± 12	Median: 2.5 Range: 0–8	-	SMT	3 T directions: 12, 6, 20, 45, 66 b: 0, 700, 1000, 2000, 3000

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TABLE 1. Continued

Author/Year	Study Design	Study Groups	Sample Size	F/M Ratio	Age (Mean ± SD)	EDSS	Disease Duration in Years (Mean ± SD)	Toolbox	Acquisition Parameters
Rahmanzadeh et al, 2022[39]	Cohort	RRMS and PPMS HC	115 (RRMS/PPMS: 76/39) 76	67/48 45/31	46 ± 14 35 ± 13	Median: 3.14 Range: 0–8	9.2 ± 10.41	SMT	3 T directions: 12, 6, 20, 45, 66 B: 0, 700, 1000, 2000, 3000
Sacco et al, 2020[40]	Cohort	RRMS, CIS, and PPMS HC	21 (RRMS/CIS/PPMS: 16/3/2) 21	17/4 17/4	36.4 ± 8.7 36.4 ± 8.7	Mean: 2.6 SD: 2.6	-	NODDI MATLAB Toolbox	3 T 30 and 64 directions b = 700, 2000
Schneider et al, 2017[16]	Cohort	RRMS HC	5 5	3/2 3/2	39.2 ± 8.6 37.6 ± 12.3	Median: 4 Range: 3–6	11 ± 3.4	NODDI MATLAB Toolbox	3 T directions: 6, 15, 30 b: 300, 711, 2000
Storelli et al, 2022[41]	Cohort	RRMS PPMS HC	43 43 55	25/18 28/15 27/28	39.48 ± 10.99 49.18 ± 10.45 41.7 ± 10.4	Median: 1.5, IQR: 1–2.5 Median: 6, IQR: 5.5–6.5	Median: 3, IQR: 1–10.6 Median: 18, IQR: 9–24.6	NODDI MATLAB Toolbox	3 T directions: 6, 30, 60 b: 700, 1000, 2855
Spano et al, 2018[42]	Cohort	RRMS SPMS HC	20 15 20	12/8 7/8 12/8	42.9 ± 6.1 50.7 ± 7.2 44.5 ± 11.7	Median: 2, Range: 1.0–4.0 Median: 5, Range: 3.5–6.5	10.3 ± 8.2 19.9 ± 9.5	AMICO	3 T directions: 30, 60 b: 711, 2855
Wu et al, 2022[43]	Cohort	RRMS HC	16 17	8/8 9/8	31.94 ± 9.72 28.04 ± 4.51	Median: 1 Range: 0–5	Median: 3.17 Range: 0.36–9.42	NODDI MATLAB Toolbox	7 T directions: 40 b: 1000, 2000, 3000
York et al, 2022[44]	Cohort	RRMS HC	60 11	46/14 7/4	Mean: 37.8, Range: 22.3–67.3 Mean: 44, Range: 27–58	Median: 2 Range: 0–6	Median: 3.55 Range: 0.2–33.2	NODDI MATLAB Toolbox	3 T directions: 151 b: 0, 200, 500, 1000, 2000

AMICO = accelerated microstructure imaging via convex optimization; CIS =clinically isolated syndrome; EDSS = Expanded Disability Status Scale; F/M = female-to-male ratio; HC = healthy control; IQR = interquartile range; MDT = Microstructure Diffusion Toolbox; MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis; N/A = not applicable; RRMS = relapsing–remitting multiple sclerosis; SD: Standard Deviation; SMT = spherical mean technique; SPMS = secondary progressive MS.

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TALE 2. Main Neuroimaging Characteristics and Cross-Sectional Findings

References	Region of Interest	NODDI Indices	Analysis Method	Findings in MS	Associations With Clinical Measures
WM lesions and NAWM					
By et al, 2017[25]	Cervical spinal cord and brain WM	ODI, ISOVF, NDI	ROI	Compared to NWM: ↑ ODI in lesions and NAWM = ISOVF in lesions and NAWM ↓ NDI in lesions = NDI in NAWM	N/a
Chen et al, 2021[18]	Brain WM	NDI, ODI, ISOVF	ROI	Compared to NWM: = NDI in NAWM = ODI in NAWM = ISOVF in NAWM Compared to NAWM: ↓NDI in lesions ↓ODI in lesions ↑ ISOVF in lesions	Significant positive associations between NAWM ODI with Timed 25-Foot Walk Test and disease duration
Collorone et al, 2020[26]	Cervical spinal cord and brain WM	NDI, ODI	ROI	Compared to NWM: ↓ NDI in brain NAWM and whole spinal cord WM = ODI in brain NAWM and whole spinal cord WM	Significant negative correlations between EDSS with NDI/ODI in the dorsal spinal cord WM
De Santis et al, 2019[28]	Brain WM	ODI, NDI	TBSS ROI	Compared to NWM: ↓ NDI in NAWM and lesions ↓ ODI in NAWM and lesions	N/a
Granberg et al, 2017[30]	Brain WM	ODI, ISOVF, NDI	Cortical surface mapping/ROI	Compared to NWM: ↓ NDI in NAWM = ODI in NAWM = ISOVF in NAWM Compared to NAWM: ↓ NDI in WM lesions ↑ ODI in WM lesions = ISOVF in WM lesions	N/a

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TALE 2. Continued

References	Region of Interest	NODDI Indices	Analysis Method	Findings in MS	Associations With Clinical Measures
Hagiwara et al, 2019[31]	Brain WM	ODI, ISOVF, NDI	TBSS ROI	Compared to NWM: ↓ ODI in WM lesions ↑ ODI in NAWM = ISOVF in WM lesions ↑ ISOVF in NAWM ↓ NDI in WM lesions = NDI in NAWM	N/a
Johnson et al, 2021[32]	Brain WM	ODI, ISOVF, NDI	VBA ROI	Compared to NWM: ↓ NDI in NAWM and lesions (results of ISOVF and ODI not reported)	Significant positive associations between NDI in NAWM/WM lesions and EDSS
Kato et al, 2022[33]	Brain WM	ODI, ISOVF, NDI	TBSS ROI	Compared to NWM: ↓ ODI in WM lesions ↑ ISOVF in WM lesions ↓ NDI in and WM lesions	N/a
Preziosa et al, 2022[36]	Brain WM	ODI, NDI	ROI	Compared to NWM: ↑ ODI in NAWM of cognitively impaired MS = ODI in NAWM of cognitively-preserved MS ↓ NDI in NAWM	WM lesion ODI can predict cognitive impairment in MS patients
Radetz et al, 2021[37]	Brain WM of the motor system	NDI, ODI, ISOVF	TBSS	Compared to NWM: ↓ NDI in NAWM ↑ ODI in NAWM = ISOVF in NAWM	N/a
Rahmanzadeh et al, 2021[38]	Brain WM	NDI	ROI	Compared to NWM: ↓ NDI in WM lesions = NDI in NAWM Compared to NAWM: ↓ NDI in WM lesions	N/a

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TALE 2. Continued

References	Region of Interest	NODDI Indices	Analysis Method	Findings in MS	Associations With Clinical Measures
Rahmanzadeh et al, 2022[39]	Brain WM	NDI	ROI	Compared to NWM and NAWM: ↓ NDI in WM lesions	N/a
Sacco et al, 2020[40]	Brain WM	NDI, ODI	ROI	Compared to NWM: ↓ NDI in NAWM and WM lesions ↑ ODI in WM lesions ↓ ODI in NAWM	N/a
Schneider et al, 2017[16]	Brain WM	NDI, ODI, ISOVF	ROI	Compared to NWM: ↓ NDI in NAWM and WM lesions ↑ ODI in NAWM ↓ ODI in WM lesions = ISOVF in NAWM ↑ ISOVF in WM lesions Compared to NAWM: ↓ NDI in WM lesions ↓ ODI in WM lesions = ISOVF in lesions	N/a
Storelli et al, 2022[41]	Brain WM	NDI	VBA	Compared to NWM: ↓ NDI in NAWM	Significant positive correlation between NDI and EDSS in the NAWM/lesion
Wu et al, 2022[43]	Brain WM	ODI, NDI	ROI	Compared to NWM: No significant differences in whole-brain WM = ODI in WM lesions ↓ NDI in WM lesions	N/a
York et al, 2022[44]	Brain WM	ISOVF, NDI	ROI	N/a (no cross-sectional finding was reported)	N/a
GM lesions and NAGM					
Barletta et al, 2021[24]	Brain GM (cortex)	NDI, ODI	Cortical Surface Mapping	Compared to NGM: = NDI and ODI measures of the NA cortex and cortical lesions Compared to NAGM:	N/a

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TALE 2. Continued

References	Region of Interest	NODDI Indices	Analysis Method	Findings in MS	Associations With Clinical Measures
				= NDI and ODI measures of the cortical lesions	
By et al, 2017[25]	Cervical spinal cord and brain GM	ODI, ISOVF, NDI	ROI	Compared to NGM: ↑ ODI in GM of patients = ISOVF in GM of patients ↓ NDI in GM of patients	N/a
Collorone et al, 2020[26]	Cervical spinal cord and brain GM	NDI, ODI	ROI	Compared to NGM: = ODI and NDI in brain NAGM and whole spinal cord GM	N/a
De Santis et al, 2019[28]	Brain GM	ODI, NDI	TBSS ROI	Compared to NGM: ↓ NDI in NAGM and lesions ↓ ODI in NAGM and lesions	N/a
Granberg et al, 2017[30]	Brain GM (cortex)	ODI, ISOVF, NDI	Cortical Surface Mapping / ROI	Compared to NGM: = NDI in the NA cortex = ODI in the NA cortex = ISOVF in the NA cortex Compared to NAGM: ↓ NDI in cortical lesions = ODI in cortical lesions = ISOVF in cortical lesions	Significant positive associations between **ODI** and EDSS in the left primary motor and somatosensory cortices
Preziosa et al, 2022[35]	Brain GM (cortex)	ODI, NDI	ROI	Compared to NGM: ↓ ODI in the NA cortex and cortical lesions ↓ NDI in the NA cortex and cortical lesions Compared to NAGM: ↓ ODI in cortical lesions ↓ NDI in cortical lesions	Significant negative correlation between **ODI** and **NDI** in NA cortex and EDSS
Preziosa et al, 2022[36]	Brain GM (cortex)	ODI, NDI	ROI	Compared to NGM: ↓ ODI in the NA cortex ↓ NDI in the NA cortex	N/a

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TALE 2. Continued

References	Region of Interest	NODDI Indices	Analysis Method	Findings in MS	Associations With Clinical Measures
Radetz et al, 2021[37]	Brain GM of the motor system (cortex)	NDI, ODI, ISOVF	TBSS	Compared to NGM: = NDI in the NA cortex = ODI in the NA cortex = ISOVF in the NA cortex	Significant positive correlation between **NDI** and of left M1 cortex and TMT-A, TMT-B, and SDMT
Rahmanzadeh et al, 2021[38]	Brain GM (cortex)	NDI	ROI	Compared to NGM: ↓ NDI in cortical lesions = NDI in NAGM Compared to NAGM: ↓ NDI in cortical lesions	N/a
GM and WM regions					
Andica et al, 2022[23]	Brain GM	NDI, ODI, ISOVF	GBSS ROI	Compared to normal tissues: ↓ NDI in the right insula and left posterior cingulate cortices ↑ ODI and ISOVF in the entorhinal, fusiform, and superior temporal regions, cerebellum cortex, lateral orbitofrontal and supramarginal regions, cingulate, hippocampus, insula, and parahippocampus	Significant positive correlations between **ISOVF/ODI** and EDSS, and MSSS in the parahippocampal region in patients with RRMS
Collorone et al, 2021[27]	Brain GM and WM	NDI, ODI	Whole Brain	Compared to normal tissues: ↓ NDI in corpus callosum NAWM, right primary visual cortex, left associative areas of the occipital lobe, left cognitive regions of the parietal lobe, and left superior-lateral temporal lobe ↑ ODI in NAWM, including the corpus callosum, occipital, frontal, and temporal WM ↓ ODI left middle frontal gyrus, left superior-lateral temporal cortex, right cognitive areas of the parietal lobe, and right operculum	Significant negative correlations between **ODI** and performance on Timed 25-Foot Walk Test within the corpus callosum

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TALE 2. Continued

References	Region of Interest	NODDI Indices	Analysis Method	Findings in MS	Associations With Clinical Measures
Gharaylou et al, 2021[29]	Brain WM	NDI, ODI	TBSS	Compared to normal tissues: ↓ NDI in widespread WM brain regions, including corticospinal tract, superior longitudinal fasciculus (temporal endings), inferior longitudinal fasciculus, inferior front-occipital fasciculus, left anterior thalamic radiation, and body of corpus callosum ↑ ODI in the body of the corpus callosum in familial MS	Significant positive correlations between **ODI** and EDSS in the corpus callosum
Hagiwara et al, 2019[31]	Brain WM	ODI, ISOVF, NDI	TBSS ROI	Compared to normal tissues: ↑ ISO in the corpus callosum, cingulate gyri, and corona radiate	N/a
Kato et al, 2022[33]	Brain WM	ODI, ISOVF, NDI	TBSS ROI	Compared to normal tissues: ↑ ISOVF in multiple WM regions ↓ NDI in multiple WM regions = ODI in multiple brain regions	N/a
Margoni et al, 2022[34]	Brain WM	NDI, ODI	TBSS	Compared to normal tissues: ↓ NDI in the superior, middle, and inferior cerebellar peduncles, cingulum, medial lemniscus, corticospinal tract, superior longitudinal fasciculus, posterior thalamic radiation, corpus callosum, fornix, and external capsule = ODI in the mentioned brain regions	N/a
Preziosa et al, 2022[36]	Brain GM and WM	ODI, NDI	ROI	Compared to normal tissues: = ODI in the thalamus ↓ NDI in the thalamus	N/a
Spano et al, 2018[42]	Brain GM	NDI, ODI	VBA	Compared to normal tissues: ↓ NDI in the tail of the hippocampus, fornix and fimbria, cingulate and lingual gyri, corpus callosum,	Negative correlations between **NDI** and EDSS and positive correlation between **NDI** and

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TALE 2. Continued

References	Region of Interest	NODDI Indices	Analysis Method	Findings in MS	Associations With Clinical Measures
				thalamus, cerebellum, and brainstem in RRMS patients ↓ NDI in pre- and postcentral gyri, inferior and orbito-frontal gyri, operculum, superior, middle and inferior temporal gyri, supramarginal and angular gyri, cuneus and precuneus, insula, lingual gyrus, parahippocampal and fusiform gyri, hippocampus, fornix and fimbria, corpus callosum, paracingulate and cingulate gyri, thalamus, internal/external capsule, caudate, putamen, cerebellum, and brainstem in SPMS patients ↑ ODI in the left supramarginal and angular gyri, in the left cingulate and paracingulate gyri, in the left corpus callosum anteriorly, in the right cingulate and precuneus gyri, and in the fornix, thalamus, and cerebellum bilaterally in RRMS patients ↑ ODI including all the mentioned anatomic regions plus the orbito-frontal gyrus, operculum, hippocampal, parahippocampal and fusiform gyri, insula, caudate, and brainstem in SPMS patients	MSFC scores in widespread brain regions Positive correlations between **ODI** and EDSS bilaterally in widespread regions Negative correlations between **ODI** and EDSS in the right caudate nucleus and thalamus

↓= reduction of NODDI metrics; ↑= increased of NODDI metrics; == null effects; b= b-value; EDSS= Expanded Disability Status Scale; GBSS= Gray Matter-Based Spatial Statistics; GM= Grey Matter; ISOVF= Isotropic Volume Fraction; MS= Multiple Sclerosis; MSFC= Multiple Sclerosis Functional Composite; MSSS= Multiple Sclerosis Severity Score; N/a= not available; NA= Normal-Appearing; NAGM= Normal-Appearing Grey Matter; NAWM= Normal-Appearing White Matter; NDI= Neurite Density Index; NODDI= Neurite Orientation Dispersion and Density Imaging; ODI= Orientation Dispersion Index; ROI= Region-Of-Interest; RRMS= Relapse-Remitting Multiple Sclerosis; SDMT= The Symbol Digit Modalities Test; SPMS= Secondary Progressive Multiple Sclerosis; T= Tesla; TBSS= Tract-Based Spatial Statistics; TMT-A= Trail Making Test part A; TMT-B= Trail Making Test part B; VBA= Voxel-Based Analysis; WM= White Matter.

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GM Lesions and NAGM

Multiple independent studies assessed GM NODDI metrics in MS and controls. These studies were performed considering both GM lesions (cortical/subcortical GM lesions identified with conventional sMRI) and NAGM. NDI of MS cortical lesions was decreased compared to the NAGM[30,35,38] of patients. Moreover, the cortical and GM (subcortical) lesions showed decreased NDI in comparison to the normal GM (NGM, referring to the GM tissue signal from healthy individuals)[28,35]; however, Barletta et al did not observe significant NDI changes in cortical lesions.[24] Analyzing NDI differences between patients' NAGM/NA cortex and normal GM from HC, four studies reported reduced values[25,28,35,36] while five reports reported null effects.[24,26,30,37,38]

Similar to what was seen in WM assessments, ODI highlighted inconsistent results. In included studies, this measure was decreased in cortical and GM lesions[28,35] and unchanged in cortical lesions[24,30] when compared with NAGM and NGM. In comparison to NGM of HC, one study showed elevated ODI of NAGM,[25] two showed null results of ODI changes in NA cortex,[24,26] and three reported decreased ODI in NA cortex and NAGM.[28,35,36] All the studies assessing ISOVF demonstrated no alterations in cortical lesions[30] and NA cortex[30,37] in affected people.

WM and GM Findings

A total of five studies included in the present systematic review assessed microstructural changes in specific NAWM regions[27,29,31,33,34] (Table 2). The corpus callosum, corticospinal tract, and superior longitudinal fasciculus were the most consistent brain regions exhibiting reduced NDI.[27,29,34] Thalamic radiation changes were also observed, as NDI of left anterior and posterior thalamic radiation was reduced.[29,34] Two of these studies also reported specific pathways, including the corpus callosum, with increased ODI.[27,29] Hagiwara et al and Kato et al focused on the ISOVF of several NAWM tracts.[31,33] Both reported higher ISOVF values within the corpus callosum and the corona radiate. However, other regions show this behavior, including the left corticospinal tract, cingulum, fornix, inferior fronto-occipital fasciculus, cerebral peduncle, and parts of the internal capsule.[33] Kato et al also reported reduced NDI in extensive NAWM regions.[33]

In addition, similar to the findings of NAWM, two studies explored specific regions of the NAGM.[23,27] Decreased NDI was observed, although mapping in different areas. Andica et al, reported GM alterations in the insula, limbic, and paralimbic regions,[23] while Collorone et al observed widespread alterations in the visual cortex, occipital, parietal, and temporal lobes.[27] ISOVF was assessed only in one study, reporting elevated values in extensive NAGM regions, including entorhinal, fusiform, and superior temporal regions, cerebellum cortex, hippocampus, insula, and parahippocampus areas.[23] In addition to these two studies, in an independent study, Preziosa et al reported that ODI thalamus of MS patients was similar to HC, while NDI was reduced.[36] Another study by Spano et al also focused on specific brain regions in affected patients.[42] However, as they reported the findings based on their clinical features, their results are provided in the next section.

Clinical MS Features and NODDI

According to Table 2, several studies enrolled patients with different MS phenotypes (RRMS, PPMS, and SPMS). Among them, three reports compared NODDI measures between MS stages.[38,41,42] NDI measure of NAWM did not show significant differences between RRMS and PPMS patients.[41] Similarly, Rahmanzadeh et al reported similar NDI values in the WM lesions of these two groups.[38] However, slightly changes were reported in PPMS patients: normal-appearing cortex exhibited lower ODI and NDI compared to RRMS,[41] suggesting potential alterations in the former group identified with NODDI metrics. This assumption was further confirmed by Spano et al, extensively exploring NODDI differences among RRMS, PPMS, and HC.[42] While MS groups exhibited similar NDI reductions in several NA brain regions (eg hippocampus, fornix and fimbria, corpus callosum, and cerebellum), ODI alterations differed between these two MS cohorts. Hippocampus, parahippocampus, superior and middle temporal gyri, cingulate and paracingulate gyri, and the anterior corpus callosum showed higher ODI values in PPMS compared to RRMS. On the contrary, the right thalamus in PPMS patients showed reduced ODI values compared with RRMS patients.[42] Overall, these findings pointed out different trajectories of microstructural alterations between PPMS and RRMS, although the limited number of studies make it difficult to infer a clear picture of the underlying alterations.

To date, only one study aimed at investigating NODDI differences between familial and sporadic MS.[29] Familial MS was defined by families with at least two members with MS, necessarily including at least one first-degree relative. NODDI in familial and sporadic MS did not differ regarding NDI and ODI values in WM regions. Further studies should investigate whether this null result would be confirmed or whether subtle differences can be detected by these groups, which might suggest different pathophysiological alterations linked with MS familiarity.

In this review, we also tackled the associations between MS clinical outcomes and NODDI measures. We identified several studies reporting this analysis.[18,23,26,27,29,32,35–37,41] The EDSS score was the most common measure investigated. A positive correlation between NDI values and EDSS in WM lesions and NAWM of MS patients was reported,[32,41] while Preziosa et al demonstrated that EDSS was negatively associated with ODI and NDI measures in the normal-appearing cortex.[35] The 25-Foot Walk Test was the second measures

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mostly assessed. The association between this score and ODI showed inconsistent results: Chen et al reported a positive correlation with NAWM,[18] while Collorone et al showed an inverse negative association with normal-appearing corpus callosum in MS patients.[27] Relationships between cognitive tests and specific WM and GM NODDI measures have been not systematically investigated. Radetz et al reported a positive association between attentional tests performance at and NDI of the motor cortex, suggesting a potential association between NODDI outcomes and cognitive abilities.[37] Furthermore, Preziosa et al explored the relationships between cognitive impairment and NODDI metrics.[36] Using the Brief Repeatable Battery of Neuropsychological Tests (BRB-N), patients were divided into two groups of cognitively impaired and cognitively preserved. Results showed that impaired MS patients had lower NAWM NDI, lower WM lesion ODI, and higher NAWM ODI compared to the preserved ones.

Finally, among all the included studies, three investigations assessed NODDI metrics in MS longitudinally.[24,40,44] Barletta et al reported stable cortical lesions NDI and in 10 RRMS patients after 1-year follow-up.[24] In contrast, Sacco et al evaluated WM lesions in a cohort of 21 MS patients at follow-up (12.6 months).[40] ODI showed longitudinal decrease in both gadolinium-enhanced and non-gadolinium-enhanced lesions, while, NDI metric showed stable results. Finally, York et al assessed WM lesion and normal-appearing tissue changes in 60 RRMS patients from baseline to 1-year follow-up.[44] Within lesions, ISOVF and NDI measures increased over time. Moreover, they reported that NDI measure of NAWM increased longitudinally, contrary to ISOVF which remained unchanged.

Discussion

This systematic review summarized the emerging NODDI literature on the MS field, suggesting microstructural changes, consistent with the histopathology and different neuroimaging techniques. Notably, significant changes in MS were observed in both lesions and the normal-appearing tissues for both WM and GM when compared to their normal counterparts. Some changes were also reported in longitudinal assessments. Moreover, although variable, NODDI metrics were linearly correlated with the clinical phenotypes. Here, we also reported MS microstructural changes during different stages.

Although MS is traditionally regarded a WM disease,[46] these findings suggest microstructural alterations in the GM. GM lesions usually show lower levels of infiltrating immune cells than WM lesions, suggesting different underlying mechanisms leading to demyelination.[47] In this review, decreased lesion NDI was the most consistent finding compared to normal or normal-appearing tissues. These findings should be interpreted in the context of the dynamic nature of the lesions and that the studies did not include patients in their relapsing phase. Dynamic interplays between acute and chronic inflammation, demyelination, and remyelination are reported in MS lesions[48] and might change NODDI patterns. As an example, acute demyelination in lesions is associated with more restricted diffusion due to the presence of inflammatory infiltrate or cytotoxic edema involving oligodendrocytes.[49]

The involvement of NAWM in MS is also characterized by diffuse inflammation, lymphocytic infiltration, and microglial activation in histological studies.[50] Moreover, the axonal loss in NAWM may be linked with direct inflammation mechanisms or secondary Wallerian degeneration from WM lesions.[51] The pattern for the NAGM is less clear. Similar to NAWM, diffuse demyelination could be found in the NAGM of people with MS,[15,52] and multimodal neuroimaging analysis reported abnormalities in both tissues.[53] In the present systematic review, we indicated all the changes in NODDI findings of NAWM and NAGM in patients. However, NAGM findings need to be interpreted with caution, as NODDI measures highly depend on the myeloarchitecture and cytoarchitecture of the GM.[54]

Among NODDI metrics, decreased NDI was considerably seen in the whole NAWM and specific regions in NAWM and NAGM (such as corpus callosum, corticospinal tracts, insula, limbic and paralimbic regions, and vast regions of cortex). This measure attributes to neuroaxonal density and myelin content[13] and its reductions might imply significant neurite loss.[55] Meanwhile, ODI showed heterogenous results both in NAWM and NAGM of patients. In contrast to NDI, it mainly reflects the morphologic changes of axons and dendrites, which is not sensitive to demyelination.[42] In NODDI, ODI changes depend on the specific brain site and axonal fractions, making it difficult to estimate ODI.[13]

NODDI could also be used to identify pathological differences between variable MS courses. It is still unknown whether MS is comprised of various diseases or whether its courses are different features of a single disease.[56] To this regard, we only reported lower ODI and NDI of the normal-appearing cortex of PPMS compared to RRMS. This is consistent with the findings of Kiljan et al, reporting axonal loss in both demyelinated and normal-appearing cortices of PPMS patients.[57] In contrast to RRMS, PPMS patients might develop cortical GM pathologies after (and maybe, independently from) WM damage, which could explain the findings of our study.[58] A preliminary report tried to assess NODDI differences between familial and sporadic MS patients, although null results were reported. Further studies might shed new light on this aspect and DWI advanced model can unravel this framework.

The findings of our study should be interpreted in the light of some limitations. First, not all studies matched patients and HC in terms of age and sex, while there is evidence of NODDI sensitivity to these two measures.[59]

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Another limitation was that not all studies recruited variable MS phenotypes (most included only RRMS) and disease durations. Finally, different scanning protocols, data acquisition methods, and hardware variations could have affected the results of each study, making the comparison more difficult.

To add to the feasibility of NODDI analysis, Caverzasi et al introduced a color-coded visualization method, making it possible to better visualize the relative weight of each diffusion compartment.[60] Although novel, NODDI itself faces limitations. For example, its metrics exhibit sensitivity, but not specificity, toward neurite spine density changes.[61] Soma and neurite density imaging (SANDI) is a recently introduced technique that can measure these aspects resulting in more specific outcomes.[62] Moreover, as previously mentioned, NODDI metrics are more specific to WM changes rather than the GM, making it necessary to introduce more novel modalities to address microstructural alterations in the affected patients' brains.[62] To achieve more reliable results in a systematic review, further studies should be performed with larger sample sizes and homogenous imaging methodologies considering the demographic characteristics of patients, disease duration, severity, courses, and medication intakes. The addition of other imaging modalities and matching histopathological studies can help cover the intrinsic limitations of NODDI as well.

Conclusions

In conclusion, our study highlights the potential of NODDI in MS. The use of advanced models for imaging analysis, such as NODDI, could help to unravel the unknown pathological mechanisms of MS enabling a deeper understanding of its pathophysiological mechanisms and disease course.

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Conflict of Interest

None.

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