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REVIEW

Neurite orientation and dispersion density imaging: clinical utility, efficacy, and role in therapy

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Abstract: In the field of diffusion magnetic resonance imaging (MRI) for neuroimaging, white matter tracts have traditionally been analyzed using diffusion tensor imaging (DTI) measures, such as fractional anisotropy. However, recent advances in diffusion MRI have provided further information on brain microstructures using multi-shell protocols of diffusion MRI. Neurite orientation dispersion and density imaging (NODDI) is one such emerging advanced diffusion MRI method that enables investigation of the neurite density and neurite orientation dispersion of brain microstructures. NODDI was developed as a practical and clinically feasible diffusion MRI technique to evaluate the microstructural complexity of dendrites and axons. This review shed light on recent studies on the use of NODDI in human brain. Indeed, a growing number of studies are using NODDI to examine neurological and psychiatric disorders, with most reporting its clinical utility. The time has thus come, for us to seriously consider the clinical use of NODDI.

Keywords: neurite orientation dispersion and density imaging, diffusion magnetic resonance imaging, brain image, neurological diseases, psychiatric disorders

Introduction

In the field of diffusion magnetic resonance imaging (MRI) for neuroimaging, white matter tracts have traditionally been analyzed using diffusion tensor imaging (DTI) measures, such as fractional anisotropy.[1] However, recent advances in diffusion MRI have provided further information on brain microstructures using multi-shell protocols of diffusion MRI, including diffusion kurtosis imaging (DKI), q-space imaging (QSI), and restriction spectrum imaging (RSI).[2–4] Neurite orientation dispersion and density imaging (NODDI) is one such emerging advanced diffusion MRI method that enables investigation of the neurite density (ND) and neurite orientation dispersion (OD) of brain microstructures.[5] Conventional DTI is based on the assumption of Gaussian distribution of diffusion processes, which may be inappropriate for non-Gaussian diffusion in biological tissues.[6] Therefore, DKI, which is a common non-Gaussian diffusion model, has been developed as the extension of DTI.[3] However, parameters derived from DKI lacked structural specificity, and for this reason, NODDI was proposed to provide more specific indices of tissue microstructures.[7] On the other hand, QSI can provide molecular displacement probability maps by using Fourier transformation,[2] but the prolonged acquisition time is problematic in clinical use.[8] RSI is a newer method than QSI or DKI, and also yields parameters of ND but not of OD.[4] Thus, NODDI is a clinically feasible technique to provide tissue-specific information based on non-Gaussian

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diffusion model. Indeed, a growing number of studies are using NODDI to examine neurological and psychiatric disorders such as Alzheimer's disease and schizophrenia.[9,10] In this article, I review the literature on recent applications of NODDI and discuss its potential clinical utility.

Principles and validations

NODDI was developed as a practical and clinically feasible diffusion MRI technique to evaluate the microstructural complexity of dendrites and axons. While OD, which represents the angular variation of neurites, can be estimated with a single high angular resolution diffusion-weighted imaging (HARDI) shell, ND requires at least two shells (ie b-values).[5] NODDI has an advantage over conventional DTI in regions with a complex microstructure and is feasible with 1.5-T MRI scanners.[11] Histopathologically, Sepehrband et al[12] reported good agreement between the fiber density estimated by NODDI and the values measured by microscopy. According to a more recent histopathological validation study,[13] NODDI can adequately describe the overall angular structures of fiber OD but fails to consistently extract discrete measures of the numbers and orientations of fiber OD peaks. Thus, although there is still room for improvement, NODDI may become a useful and reliable method for further investigating the microstructural complexity of the brain.

Alzheimer's disease

Alzheimer's disease is the most common cause of dementia. Early detection of Alzheimer's disease is clinically important in terms of early cognitive intervention[14,15,16] as well as future development of disease-modifying therapy,[17] and neuroimaging plays key roles in ensuring accurate and early diagnosis, in revealing the underlying pathophysiology, and in monitoring the disease. Thus far, the use of NODDI in Alzheimer's disease has focused on young-onset Alzheimer's disease (Table 1).[10,18] Using NODDI, Slattery et al[10] reported an association between white matter changes and apolipoprotein E (APOE) ε4 status, which is the main inherited risk factor for sporadic Alzheimer's disease. They also revealed correlations between regional white matter ND and neuropsychological batteries. Another study of young-onset Alzheimer's disease and NODDI reported a widespread reduction in cortical ND and OD, including mesial and lateral temporal lobe and precuneus.[18] Moreover, Fu et al[19] reported that ND has detected clearer differences between Alzheimer's disease and mild cognitive impairment than FA. Thus, NODDI may have better sensitivity to diagnose Alzheimer's disease than conventional DTI.

Parkinson's disease

Parkinson's disease is a common neurodegenerative movement disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra, and the overall prevalence is approximately 300–500 per 100,000 people.[20] Through the use of NODDI, Kamagata and colleagues[21] first unveiled reduced ND in the substantia nigra and putamen in patients with Parkinson's disease, which correlated with disease severity. Subsequently, the same group also reported detection of gray matter abnormalities by NODDI and its diagnostic accuracy, as well as retrograde degeneration of the nigrostriatal pathway in patients with Parkinson's disease.[22,23] Thus, NODDI may prove to be useful in the diagnosis and monitoring of Parkinson's disease. Especially, the potential of early detection has been suggested.[7]

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease involving damage to the myelin sheaths of the brain and spinal cord, and the global median prevalence is 33 per 100,000 people.[24] In NODDI, the demyelinating lesions in white matter are detected as decreased ND (Figure 1). Schneider and colleagues[25] reported more sensitive detection of MS lesions with NODDI parameters than with conventional DTI. Similar findings were also reported for spinal lesions.[26] In contrast, the cortical lesions of MS are more subtle and difficult to detect on conventional MRI. Accordingly, the finding of reduced ND even in cortical lesions[27] may have further clinical implications for MS. Additionally, the further usefulness of NODDI was indicated for detecting the disease progression of MS, including the change from normal-appearing white matter to lesions.[28,29] The viability of a 7-T MRI scanner was also confirmed in MS.[30]

Epilepsy

Epilepsy is a common neurological disease marked by recurrent seizures associated with abnormal electrical activity in the brain. Patients with drug-resistant focal seizures can benefit from neurosurgical resection, and successful localization of the focus is thus a key clinical role of neuroimaging in epilepsy. For focal epilepsy, Winston et al[31] reported the clinical usefulness of reduced ND in focal cortical dysplasia, which was also visible on conventional MRI. Subsequently, a significant reduction in ND was revealed in temporal lobe

Table 1 NODDI findings in Alzheimer's disease, Parkinson's disease, multiple sclerosis, and epilepsy

	Target	Study population	Tesla	b-values	Directions	Main findings relevant to NODDI
Alzheimer's disease						
Slattery, et al 2017[10]	AD	37YOAD, 23HV	3	300, 700, 2000	8, 32, 64	Association with APOEε4 status. Regional ND was correlated with cognition.
Parker, et al 2018[18]	AD	38YOAD, 22HV	3	300, 700, 2000	8, 32, 64	OD↓, widely ND↓ in cortex
Fu, et al 2019[19]	AD, MCI	14AD, 14MCI, 14HV	3	1000, 2000	64 each	OD↓, widely ND↓. Better diagnosis than FA
Parkinson's disease						
Kamagata, et al 2016[21]	PD	58PD, 36HV	3	1000, 2000	32 each	ND↓ in SN and putamen. Correlation with severity.
Kamagata, et al 2017[22]	PD	30PD, 28HV	3	1000, 2000	32 each	ND↓ in gray matter. Better diagnostic value.
Andica, et al 2018[23]	PD	29PD, 29HV	3	1000, 2000	32 each	ND↓ in nigrostriatal pathway.
Multiple sclerosis						
Schneider, et al 2017[25]	MS	5MS, 5HV	3	300, 711, 2000	6, 15, 30	Greater specificity than DTI parameters.
Granberg, et al 2017[27]	MS	26MS, 24HV	3	1000, 5000	64, 128	ND↓ in cortical lesion. ND↓/OD↑ in white matter lesion.
By, et al 2017[26]	MS (spine)	6MS, 8HV	3	711, 2855	32, 64	ND↓ in lesion
Spano, et al 2018[28]	MS	20RRMS, 15SPMS, 20HV	3	711, 2855	30, 60	ND↓ and OD↑. SPMS showed more widespread abnormalities
De Santis et al 2019[30]	MS	7MS, 6HV	3, 7	700, 2000	27, 45	Specificity↑, Sensitivity↑ by NODDI. 7-T NODDI viable.
Mustafi, et al 2019[29]	MS	6MS	3	250, 1000, 2250, 4000, 6250	6, 21, 24, 30, 61	Microstructural alterations from normal-appearing white matter to peri-lesion areas and lesions
Epilepsy						
Winston et al 2014[31]	FE	5FE	3	700, 2000	24, 48	ND↓ in focal lesion.
Lemkaddem, et al 2014[35]	TLE	22TLE, 21HV	3	Up to 6400	128 in total	Impaired connectivity.
Rostampour, et al 2018[33]	FE	17FE	3	700, 2000	30, 64	Abnormal OD in 8 patients.
Sone, et al 2018[32]	TLE	33TLE, 33HV	3	1000, 2000	32 each	ND↓ in focus side.
Sone, et al 2018[36]	IGE	14IGE, 16HV	3	1000, 2000	16 each	OD↓ in mediofrontal area.

Abbreviations: AD, Alzheimer's disease; FE, focal epilepsy; HV, healthy volunteers; IGE, idiopathic generalized epilepsy; MCIm, mild cognitive impairment; MS, multiple sclerosis; PD, Parkinson's disease; RRMS, relapsing-remitting MS; SN, substantia nigra; SPMS, secondary progressive MS; TLE, temporal lobe epilepsy; YOAD, young-onset AD.

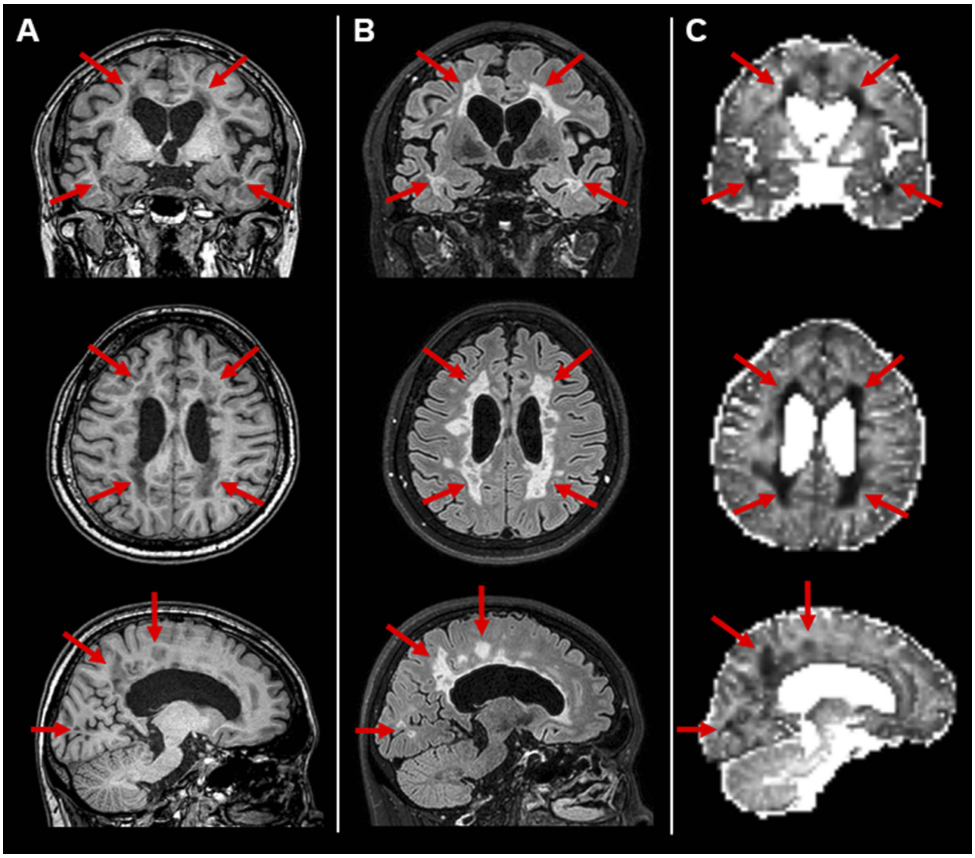

Figure 1 Sample images (**A**, T1-weighted; **B**, FLAIR; **C**, neurite density) of a 48-year-old patient with relapsing-remitting multiple sclerosis. Reduced neurite density can be seen in the demyelinating white matter lesions (arrows).

epilepsy without visible lesions on conventional MRI.[32] Additionally, hippocampal sclerosis, which is the most common cause of temporal lobe epilepsy, shows reduced ND and OD.[32] Representative images of these findings are shown in Figure 2. Cortical abnormalities on OD images in focal epilepsy have also been reported,[33] but a limitation was raised afterward.[34] At any rate, these findings would suggest a potential use for NODDI as a novel clinical biomarker for focal epilepsy treatment. Apart from focus detection, NODDI has revealed a brain connectivity dysfunction in temporal lobe epilepsy[35] and a frontal lobe abnormality in idiopathic generalized epilepsy.[36]

Stroke

In the field of stroke, NODDI is mainly being investigated for its ability to predict and monitor recovery after stroke (Table 2). The global prevalence of stroke is approximately 500 per 100,000 people and it increases up to 4,835 in the elderly.[37] To achieve a better course of treatment, prognosis of post-stroke recovery is desirable but still imprecise.[38] Diffusion MRI is an expected biomarker,[39] and thus NODDI may expand the predictability by providing additional information on microstructural complexity after stroke. An initial preliminary study showed greater specificity of NODDI for white matter reconstruction after brain infarction.[40] Subsequently, Hodgson et al[41] showed the usefulness of NODDI for predicting upper extremity motor function recovery after stroke, by investigating NODDI parameters within the corticospinal tracts. Another study revealed an increase of OD in the ipsilateral corticospinal tract in subacute stroke, which persisted in the chronic phase.[42] Additionally, NODDI was reported to have improved sensitivity for detecting microstructural changes in the brain during ischemic stroke compared with DTI and DKI.[43] Beyond usual stroke, Hara et al[44] investigated patients with moyamoya disease, which is a progressive cerebrovascular disease caused by blocked main arteries of the brain, and found that NODDI parameters are significantly correlated with PET and clinical severity.

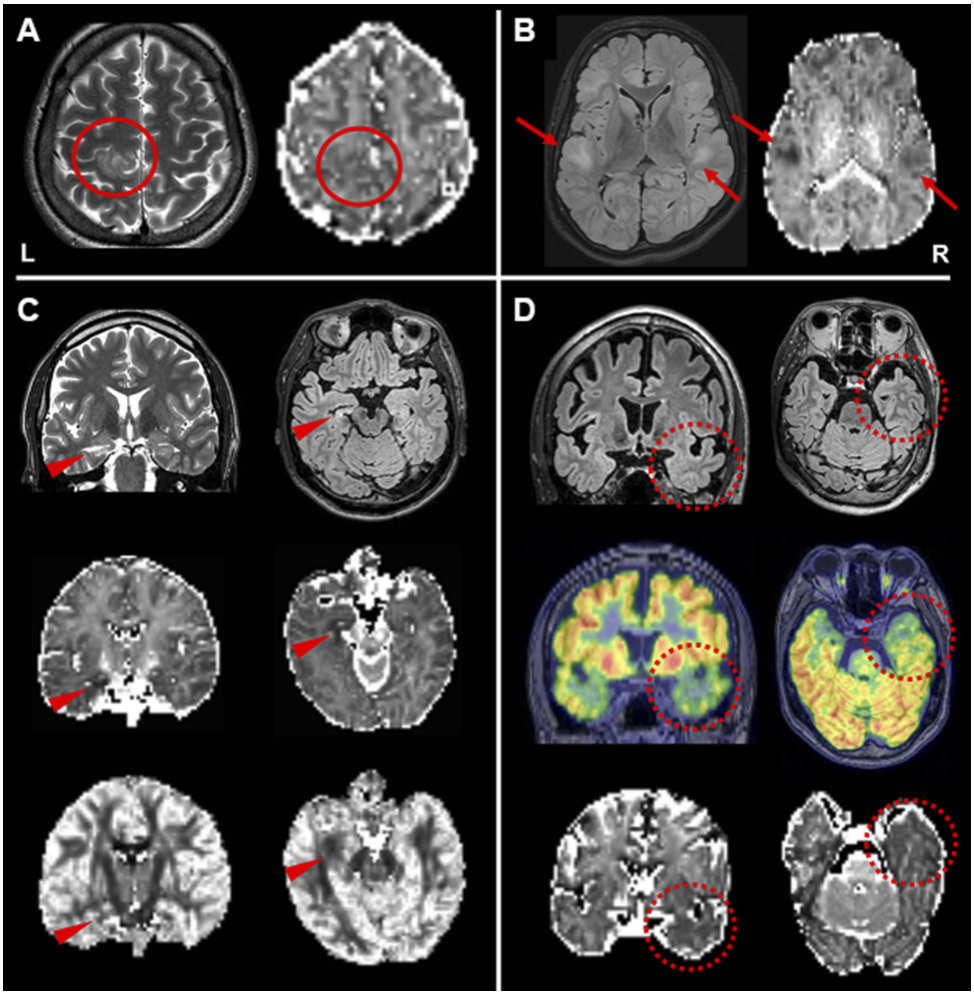

Figure 2 (**A**) In a 46-year-old patient with focal epilepsy, reduced neurite density is evident in the focal cortical dysplasia (circles). (**B**) A 17-year-old patient with tuberous sclerosis. Reduced neurite density can be seen in the multiple cortical tubers (arrows). (**C**) A 37-year-old patient with left temporal lobe epilepsy and hippocampal sclerosis. The abnormal hippocampus shows reduced neurite density and orientation dispersion (arrowheads). (**D**) A 47-year-old patient with right temporal lobe without any visible lesions on conventional MRI. The right temporal lobe shows reduced neurite density in accordance with the hypometabolic areas of ^{18}F-FDG-PET (broken circles).

Tumors

The clinical application of NODDI is also expected in the field of brain tumors, particularly for differentiating gliomas. After the discovery of unique contrast of NODDI maps within gliomas with a 7-T MRI scanner,[45] Maximov et al[46] reported the reliable and feasible differentiation of glioma grading by NODDI parameters. Additionally, although there is no significant additional utility of NODDI for detecting isocitrate dehydrogenase-1 (IDH-1) mutation status in gliomas,[47,48] quantitative NODDI metrics in tumoral and peritumoral regions are suggested to be useful for glioma grading.[48] ND seems to have the best discriminative power for distinguishing normal, tumoral, and peritumoral edematous areas.[49] In addition, Kadota and colleagues[50] showed a potential differentiation between glioblastoma and solitary metastasis with NODDI.

Trauma

For the use of NODDI in traumatic brain injury, Wu et al[51] demonstrated improved sensitivity of the NODDI parameter (axonal density) for white matter changes shortly after mild traumatic brain injury. Additionally, Churchill et al[52] reported a reduced ND and increased OD index in athletes with concussion. Afterward, the same group also found NODDI abnormalities at both phases in injury and recovery from concussion using longitudinal data.[53] These findings may help us to understand the microstructural complexity of brain injuries over time.

Psychiatric disorders

Psychiatric disorders are also an important clinical target of advanced neuroimaging modalities. For NODDI, Nazeri and colleagues[9] found significantly lower ND in gray

Table 2 NODDI findings in stroke, tumor, and trauma

	Target	Study population	Tesla	b-values	Directions	Main findings relevant to NODDI
Stroke						
Adluru, et al 2014[40]	Stroke	2 strokes	3	500, 1000, 2000, 5000	20, 30, 64, 64	Specific marker for reconstruction in recovery
Hodgson, et al 2019[41]	Stroke	9 strokes, 9HV	3	Up to 4000	203 in total	More predictive of motor outcome.
Wang, et al 2019[43]	Stroke	71 strokes	3	1250, 2500	25 each	ND↑, OD↑. OD correlated with duration.
Mastropietro, et al 2019[42]	Stroke	17 strokes	3	700, 2000	20, 64	OD↑ in ipsilateral corticospinal tract.
Hara, et al 2019[44]	Moyamoya	33MMD, 20HV	3	700, 2850	30, 60	Correlation with PET and severity.
Tumor						
Wen, et al 2015[45]	Glioma	20 gliomas, 5HV	7	1000, 2000	30, 60	Unique contrast reflecting microstructure.
Maximov, et al 2017[46]	Glioma	24 gliomas	3	1000, 2500	60 each	Effectively used as glioma grade biomarkers.
Figini, et al 2018[47]	Glioma	192 gliomas	3	700, 2000	20, 40	Correlation with isocitrate dehydrogenase status. No additional value to DTI.
Zhao, et al 2018[48]	Glioma	42 gliomas	3	1000, 2000	30 each	Highly valuable for glioma grading.
Kadota, et al 2018[50]	GB&Meta	9GB, 6Meta	3	1000, 2000	32 each	Extra cellular volume fraction ↑ in GB
Masjoodi, et al 2018[49]	Edema	12 tumors	3	1000, 2000	30, 64	ND had the best distinguishing normal tumoral and edematous areas
Trauma						
Wu, et al 2018[51]	Mild TBI	19mTBI, 23Ctrl	3	250, 1000, 2250, 4000, 6250	6, 21, 24, 30, 61	Only intra-axonal volume fraction showed significant group difference.
Churchill, et al 2017[52]	Concussion	31concussion, 37Ctrl	3	700, 2000	30, 64	ND ↑, OD↓ in concussion.
Churchill, et al 2019[53]	Concussion	33concussion, 33Ctrl	3	700, 2000	30, 64	Intra-neurite water volume ↓, in both injury and recovery phases.

Abbreviations: Ctrl, controls; GB, glioblastoma; HV, healthy volunteers; Meta, metastasis; MMD, moyamoya disease; mTBI, mild traumatic brain injury.

matter in the temporal pole, anterior parahippocampal gyrus, and hippocampus of patients with schizophrenia. Additionally, significantly reduced fractional anisotropy and ND in several white matter tracts were also reported in patients with first-episode psychosis.[54] In schizophrenia, another study showed increased OD in the posterior limb of internal capsule and negative correlation with subsequent drug response.[55] Moreover, Spray et al[56,57] reported correlations between OD and hallucination proneness in otherwise healthy individuals. For mood disorders, reduced ND and OD were found in major depressive disorder with a correlation between OD and disease severity.[58] In bipolar affective disorder, Ota et al[59] reported reduced ND in the right posterior cingulate cortex, although a previous study did not find any significant changes in bipolar affective disorder.[9] This discrepancy could be related with treatment, since another study reported that patient with bipolar affective disorder without lithium therapy showed lower ND in the left frontal cortex than those with lithium as well as than healthy controls.[60] Thus, there are already several studies of NODDI and several common psychiatric disorders, suggesting a future clinical use for NODDI. However, psychiatric disorders and symptoms are highly diverse and remain to be fully elucidated in neuroimaging studies.

Brain development

NODDI is also suggested to be useful for estimating brain development from the neonatal period to adulthood (Table 3). In healthy infants, NODDI in combination with myelin content information may provide a good indicator of brain myelination with age.[61] In addition, in preadolescence, ND is strongly correlated with age in many brain regions, showing an even better correlation than fractional anisotropy.[62] Age-related increases of ND were also reported during late childhood and adolescence, suggesting axonal packing in this term.[63] For adults, Nazeri and colleagues[64] revealed age-related OD decreases in frontoparietal regions and increases in the hippocampus, as well as a relationship with executive function. Ota et al[65] also reported age-related changes in healthy adults in terms of NODDI and DTI/DKI parameters.

As a comparison with normal development, several developmental abnormalities have been investigated by NODDI. In preterm and very preterm children, NODDI detected several regional microstructural changes, partly associated with language function or intelligence quotient.[66,67,68] Additionally, Karmacharya, et al investigated neonates with congenital heart disease and reported bilateral reduction in several tracts.[69] In developmental dyslexia, age-related differences in local gyrification were correlated with NODDI parameters.[70] Thus, NODDI may enable us to investigate human brain development, aging, and developmental disorders in greater detail.

Other brain disorders

There are many applications of NODDI in other brain disorders (Table 4). Broad et al[71] found reduced ND in extensive regions of the corticospinal tract in amyotrophic lateral sclerosis, which is consistent with the core pathology of these areas. The corticospinal tract is also a target of research in idiopathic normal pressure hydrocephalus.[72,73] In the corticospinal tract, ND and OD are reduced in idiopathic normal pressure hydrocephalus,[72] and axon density was unchanged after surgical treatment.[73] In preclinical Huntington's disease, widespread reductions in axonal density have already been found and correlated with clinical disease progression.[74] Song et al[75] used NODDI to investigate patients with Wilson disease and found a significant reduction in ND and OD in the basal ganglia and thalamus. In galactosemia, ND was decreased in bilateral anterior areas and OD was increased in the left hemisphere.[76] Another study investigating patients with diabetes mellitus and mild cognitive impairment reported reduced ND and its correlations with the hemoglobin A1C level, disease duration, and neuropsychological scores.[77] The effect of systemic medical conditions on the brain was also investigated using NODDI for hypertension,[78] sickle cell anemia,[79] and interferon-alpha–induced fatigue.[80] Abnormal NODDI parameters were also reported in patients with myalgic encephalomyelitis/chronic fatigue syndrome.[81] Billiet and colleagues[82] found reduced ND in the "unidentified bright objects" in neurofibromatosis type 1. Other studies focused on perinatal encephalopathy,[83] SYN1Q555X mutation,[84] C9orf72 disease,[85] and sarcoma survivors.[86]

Spine

NODDI is also feasible for evaluating the human spinal cord.[87] In addition to its use for the spinal lesions of MS,[26,88] some studies have focused on cervical spondylotic myelopathy.[89,90,91] In general, ND showed good correlations with disease severity. In particular, preoperative ND may be a strong indicator of neurological dysfunction and postoperative recovery in cervical spondylotic myelopathy.[91]

Table 3 NODDI findings in psychiatry and brain development

	Target	Study population	Tesla	b-values	Directions	Main findings relevant to NODDI
Psychiatry						
Nazeri, et al 2017[9]	SC, BPAD	36SC, 29BPAD, 35HV	3	1000, 3000, 4500	30 each	ND↓ in SC. Intermediate findings in BPAD. Correlation with spatial working memory.
Rae, et al 2017[54]	FEP	35FEP, 10HV	1.5	300, 800, 2400	9, 30, 60	ND↓ in FEP. OD↑ along with aging in FEP.
Spray, et al 2018[56]	Hallucination	38HV	3	1000, 2000	60 each	OD correlated with hallucination proneness
Spray, et al 2018[57]	Hallucination	25HV	3	1000, 2000	60 each	OD correlated with hallucination proneness
Ota, et al 2018[58]	MDD	23MDD, 26HV	3	1000, 2000	16 each	ND↓, OD↓ in MDD.
Ota, et al 2019[59]	BPAD	31BPAD, 28HC	3	1000, 2000	16 each	ND↓, OD↓ in BPAD.
Sarrazin, et al 2019[60]	BPAD	41BPAD, 40HV	3	200, 1500, 2700 600, 1000, 1400	30, 60, 60 30, 30, 30	ND↓ in BPAD without lithium than HV and BPAD with lithium.
Kraguljac, et al 2019[55]	SC	42SC, 42HV	3	1000	30	OD↑ in SC. Correlation with drug response.
Brain development						
Nazeri, et al 2015[64]	Healthy	45HV	3	1000, 3000, 4500	30 each	Age-related changes of OD.
Dean, et al 2016[61]	Healthy	18HV(children)	3	700, 2000	30 each	Good indicator for brain myelination
Mah, et al 2017[62]	Healthy	27HV(children)	3	900, 2000	30 each	ND strongly correlated with age
Ota, et al 2017[65]	Healthy	23HV	3	1000, 2000	16 each	ND correlated with age
Eaton-Rosen, et al 2015[66]	Preterm	12 preterm	3	750, 2000	16, 32	Region-dependent changes over preterm period
Murner-Lavanchy, et al 2018[67]	Very preterm	145 very preterm, 33 term-born	3	1200, 3000	25, 45	Axon density ↑, associated with semantic performance.
Karmacharya, et al 2018[69]	CHD	19CHD, 16HV	3	1000, 2000	30 each	ND↓ in neonates with CHD
Caverzasi, et al 2018[70]	DD	39DD, 56TD	3	700, 2000	30, 64	Correlation with age-related gyrification.
Geeraert, et al 2019[63]	Healthy	48HV(children)	3	900, 2000	30 each	Age-related ND↑
Young, et al 2019[68]	Very preterm	23 very preterm, 24 term-born	3	700, 1000, 2850	60 each	OD↑ in very preterm. ND correlated with IQ.

Abbreviations: BPAD, bipolar affective disorder; CHD, congenital heart disease; DD, developmental dyslexia; FEP, first episode psychosis; HV, healthy volunteers; IQ, intelligence quotient; MDD, major depressive disorder; SC, schizophrenia; TD, typical development.

Table 4 NODDI findings in other brain diseases and spine

	Target	Study population	Tesla	b-values	Directions	Main findings relevant to NODDI
Others (brain)						
Billiet, et al 2014[82]	NF1	17NF1	3	700, 1000, 2800	25, 40, 75	ND↓ in unidentified bright objects in NF1
Timmers, et al 2015[76]	Galactosemia	8 galactosemia, 8HV	3	1000, 2000	64 each	ND↓. Correlation with behavioral outcome.
Kansagra, et al 2016[83]	Encephalopathy	25 encephalopathy	3	700, 2000	30, 55	More details of microstructural maturation
Suzuki, et al 2017[78]	Hypertension	2337HT, 2322non-HT	3	1000, 2000	100 in total	ND↓ in HT
Irie, et al 2017[72]	iNPH	19iNPH, 12HV	3	500, 1000, 1500, 2000, 2500	32 each	ND↓, OD↓ in corticospinal tract.
Kamiya, et al 2017[73]	iNPH	10iNPH, 14HV	3	500, 1000, 1500, 2000, 2500	32 each	Axon density ↓, unchanged after surgery.
Zhang, et al 2018[74]	HD	38pre-HD, 45HV	3	300, 700, 2000	8, 32, 64	Axon density ↓, correlation with progression.
Song, et al 2018[75]	WD	24WD, 25HV	3	1000, 2000	30 each	ND↓, OD↓ in BG and thalamus.
Stotesbury, et al 2018[79]	Sickle cell anemia	46PT, 32Ctrl	3	1000, 2200	N/A	Correlation with processing speed.
Cabana, et al 2018[84]	SYN1Q555X	13 carriers, 13HV	3	300, 1000, 2000	8, 32, 60	Alterations in language-related regions.
Sleurs, et al 2018[86]	Sarcoma survivor	34 sarcoma survivors, 34HV	3	700, 1000, 2800	25, 40, 75	NODDI abnormalities suggesting chemotherapy-related changes.
Broad, et al 2019[71]	ALS	23ALS, 23HV	1.5	300, 800, 2400	9, 30, 60	ND↓ in corticospinal tract, etc.
Kimura et al 2019[81]	ME/CFS	20ME/CFS, 23HV	3	1000, 2000	32 each	ND↓, OD↓↑ in ME/CFS
Dowell, et al 2019[80]	IFN-α fatigue	18 IFN-α treated PT	1.5	300, 800, 2400	8, 30, 60	ND↑ in IFN-α-induced fatigue
Xiong, et al 2019[77]	DM-MCI	20DM-MCI, 18DM-NC, 28HV	3	1250, 2500	25 each	ND↓ in DM-MCI
Wen, et al 2019[85]	C9orf72	38 carriers, 29HV	3	300, 700, 2200	9, 32, 60	ND↓ in 10 tracts.
Spine						
Jiang, et al 2018[89]	CSM	57 postoperative CSM	3	1000, 2000	32 each	ND correlated with severity.
Ma, et al 2018[90]	CSM	58 postoperative CSM	3	1000, 2000	32 each	ND correlated with severity.
Okita, et al 2018[91]	CSM	27 pre/post CSM	3	500, 1000, 2000, 3000	6 each	Preoperative ND correlated with outcomes

Abbreviations: ALS, amyotrophic lateral sclerosis; BG, basal ganglia, CSM, cervical spondylotic myelopathy; Ctrl, controls; DM-MCI, diabetes mellitus with mild cognitive impairment; DM-NC, diabetes mellitus with normal cognition; HD, Huntington's disease; HT, hypertension; HV, healthy volunteers; IFN, interferon; iNPH, idiopathic normal pressure hydrocephalus; ME/CFS, myalgic encephalitis/chronic fatigue syndrome; N/A, not available; NF1, neurofibromatosis 1; PT, patients; WD, Wilson's disease.

Future directions

Because the number of studies of NODDI is increasing, we should seriously consider the use of NODDI in daily clinical practice. However, there are several issues to be addressed. First, the MRI protocols and scanners are still inconsistent, and no standards have been established. To achieve the clinical utility of NODDI across different institutes, standard settings should be needed. Although optimal b-values and more directions may yield better images, a clinical protocol with a shorter acquisition time is preferable. Second, we have to consider which NODDI parameters to use. Beyond ND and OD, we can also obtain more advanced metrics such as axon density. Similarly, regarding the targeted areas of brain (eg gray matter or white matter tract), there's some variability among studies. We may need to understand the basic and clinical meanings of these parameters to correctly interpret patients' findings. Third, most of the clinical studies on NODDI are from single centers and have not been reproduced in other studies. Novelty is an important consideration for study and publication, but clinical application also strongly requires further accumulation of evidence from repeated confirmation of results.

In addition, there are some useful tools or improved methodologies. Cacerzasi et al[92] reported the use of color maps of NODDI for the visual assessment of several neurological diseases. On the other hand, the criticisms to NODDI are mainly associated with the bias derived from the fitting model and its assumption.[93,94,95] To overcome this limitation, there are improved methodologies for diffusion MRI, such as NODDI with diffusivity assessment (NODDIDA),[94] spherical mean technique (SMT),[95] NODDI-DTI model[96] and gamma metrics.[97] These methodological advances may also deepen our basic and clinical knowledge and promote the clinical use of NODDI.

Conclusion

This review shed light on recent studies on the use of NODDI in humans. The number of studies using NODDI is growing, with most reporting its clinical utility. The time has thus come for us to seriously consider the clinical use of NODDI. Especially, NODDI may directly affect the treatment and recovery prediction in several diseases including stroke, epilepsy and glioma. Setting standard protocols and parameters will accelerate the clinical applications and highly benefit patients with neurological and psychiatric disorders.

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Disclosure

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