

Neurite Orientation Dispersion and Density Imaging in Psychiatric Disorders: A Systematic Literature Review and a Technical Note

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ABSTRACT

While major psychiatric disorders lack signature diagnostic neuropathologies akin to dementias, classic postmortem studies have established microstructural involvement, i.e., cellular changes in neurons and glia, as a key pathophysiological finding. Advanced magnetic resonance imaging techniques allow mapping of cellular tissue architecture and microstructural abnormalities *in vivo*, which holds promise for advancing our understanding of the pathophysiology underlying psychiatric disorders. Here, we performed a systematic review of case-control studies using neurite orientation dispersion and density imaging (NODDI) to assess brain microstructure in psychiatric disorders and a selective review of technical considerations in NODDI. Of the 584 potentially relevant articles, 18 studies met the criteria to be included in this systematic review. We found a general theme of abnormal gray and white matter microstructure across the diagnostic spectrum. We also noted significant variability in patterns of neurite density and fiber orientation within and across diagnostic groups, as well as associations between brain microstructure and phenotypical variables. NODDI has been successfully used to detect subtle microstructure abnormalities in patients with psychiatric disorders. Given that NODDI indices may provide a more direct link to pathophysiological processes, this method may not only contribute to advancing our mechanistic understanding of disease processes, it may also be well positioned for next-generation biomarker development studies.

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Psychiatric disorders are highly prevalent and carry a significant personal and public health burden (1,2). The negative effects of these disorders are not only apparent for a patient's well-being and quality of life (3), they are also expressed through reduced life expectancy and increased mortality (4,5). While the development of a broad range of psychotropic pharmaceuticals has revolutionized the field, efficacy of available drugs is limited and curative treatments remain elusive (6). An important factor contributing to this reality is that our understanding of the causes and mechanisms underlying psychiatric disorders, a prerequisite for targeted drug development, remains limited (7).

Postmortem studies have established microstructural involvement, i.e., cellular changes in neurons and glia, as a key pathophysiological finding in major psychiatric disorders (8–11). In parallel, diffusion tensor imaging (DTI) has been critical in confirming the presence of microstructural abnormalities *in vivo*, albeit without neuropathological specificity (12). For example, fractional anisotropy, a popular DTI-derived metric, can be reduced in the presence of axonal loss, reduced orientational coherence of the axons, or cerebrospinal fluid (CSF) contamination. To address this limitation, newer diffusion magnetic resonance imaging (MRI) techniques are aimed at the *in vivo* evaluation of cellular tissue architecture, mapping histological features non-invasively. One increasingly popular technique, neurite

orientation dispersion and density imaging (NODDI) (13), enables the estimation of three key aspects of neuronal tissue for each voxel: neurite density index (NDI), which quantifies the packing density of axons or dendrites; orientation dispersion index (ODI), which assesses the orientational coherence of neurites; and the free water fraction (FWF), which estimates the extent of CSF contamination. Histological validation studies of NODDI have provided evidence that ODI matches its histological counterpart (14–18) and similarly for NDI (16,19). Findings from a transgenic Alzheimer's disease model charting the evolution of diffusion-derived markers found that changes in FWF are consistent with the evolution of an inflammatory response, supporting the interpretation of FWF as a proxy of inflammation (20).

We discuss essential principles and relevant technical considerations and provide recommendations for implementation of NODDI to study brain microstructure in psychiatric disorders. To provide a synopsis of the current state of the relevant literature, we also conducted a systematic review of studies assessing NODDI abnormalities in psychiatric disorders. We hypothesized that alterations in brain microstructure would be evident in all psychiatric disorders. However, given the known heterogeneity within and across diagnostic constructs and the variability in data acquisition and analysis approaches, we expected that findings of NODDI abnormalities would differ between studies.

METHODS

Selective Review of Technical Considerations in NODDI

The first part of this article describes a selective review of key principles of NODDI and technical considerations in its application to the study of brain microstructure in psychiatric disorders.

Systematic Review of Applications of NODDI in Psychiatric Disorders

Eligibility Criteria. We included studies that used NODDI to assess brain microstructure in psychiatric disorders published between January 2012 and July 2021 (date of last search: September 28, 2021). We excluded review articles, studies published in languages other than English, and studies with nonhuman subjects. Studies expressly including subjects with neurologic or genetic diseases or intellectual disabilities were not considered (Figure 1).

Literature Search and Study Selection. Using PubMed, we used the following search term: “(NODDI OR neurite density OR orientation dispersion) AND (mental disorder OR psych* OR schizo* OR bipolar OR depress* OR mood OR mania OR OCD OR anxiety OR PTSD OR substance OR SUD OR addiction OR eating disorder OR anorexia OR bulimia OR attention-deficit OR autism).” We used the following filters to narrow the search: date range, January 1, 2012, to September 28, 2021; species, humans; and language, English. After removal of duplicate articles, titles and abstracts retrieved from the search were reviewed, and potentially eligible studies were selected for full text review. At this stage, we first removed review articles/commentaries and case reports, then post-mortem and preclinical studies, then method development manuscripts and studies that did not use NODDI, and finally studies conducted in populations without psychiatric disorders, comorbid medical conditions, and genetic syndromes. Full texts were obtained and eligibility criteria were applied to

the articles. Reference lists of those studies and major review articles of the NODDI literature were inspected for additional relevant publications.

Data Extraction. Two authors (NVK and MJS) extracted the following data for each study independently: name of first author, year of publication, number of participants per diagnostic category, diagnostic categories, demographic variables, illness duration, use of psychotropic medications, data acquisition parameters, NODDI indices used, analysis methods, regions of interest, main study outcomes, and associations between NODDI indices and clinical variables. The final summary table was developed in consensus.

RESULTS

Selective Review of Technical Considerations in NODDI

Key Assumptions of the NODDI Model. NODDI belongs to the family of diffusion MRI techniques underpinned by multicompartment models (21). Multicompartment models interpret the MRI signals in each voxel as the sum of the contributions from the individual compartments that make up the voxel. This interpretation of the voxelwise MRI signals confers the fundamental advantage over the standard DTI and the more recent diffusion kurtosis imaging (22). The metrics provided by DTI or diffusion kurtosis imaging can only provide a composite view of the multifaceted contributions in a voxel. As a result, a change to DTI-derived fractional anisotropy, as highlighted above, may be caused by a host of underlying changes to the contributing compartments. In contrast, multicompartment models aim to disentangle the contribution from each compartment, thereby enabling their individualized characterization. This distinction between DTI/diffusion kurtosis imaging and NODDI is illustrated in Figure 2.

Among multicompartment models, a key distinguishing feature of the NODDI model is the number of compartments assumed to be present within a voxel. Most models contemporaneous with NODDI adopt a two-compartment representation of neural tissue, with one compartment representing the signal contribution from water confined in the intraneurite space and the other capturing the contribution from the water in the extraneurite space. However, this approach does not account for the potential contribution from CSF contamination, which is non-negligible for cortical gray matter, periventricular subcortical gray matter, and white matter. To address this, NODDI additionally includes a third compartment, enabling CSF contamination to be explicitly accounted for. The detail of the NODDI model is illustrated in Figure 3. It shows the two key metrics provided by the NODDI model: f_{fw} , the FWF, and f_{in} , the NDI. It also shows the assumptions made for each compartment and the parameters that the model requires known a priori. First, the intraneurite compartment models the space within individual neurites, which is approximated as a collection of sticks. One of its parameters is d_{in} , the rate of diffusion along individual neurites. This parameter is empirically estimated to be $1.7 \mu\text{m}^2/\text{ms}$ and is assumed to be the same for different brain regions and for different subjects (23). Guerrero *et al.* (24) have investigated the influence of fixed diffusivity

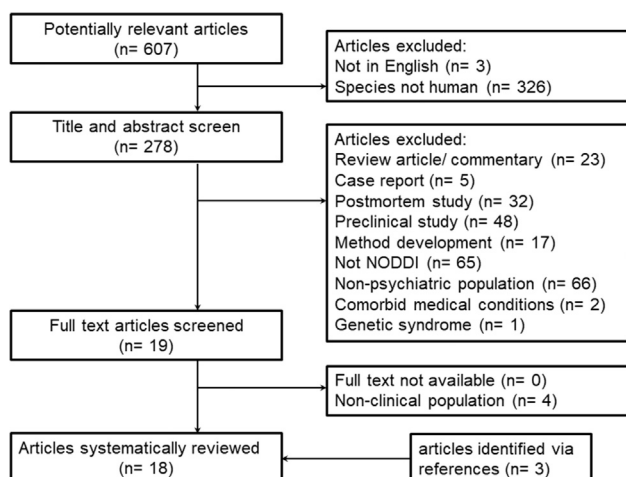


Figure 1. Process of study inclusion. NODDI, neurite orientation dispersion and density imaging.

NODDI Alternative to DTI

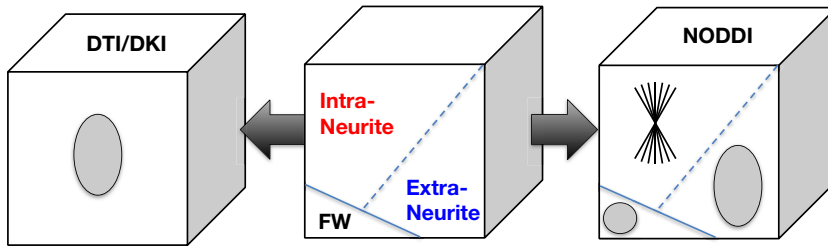


Figure 2. While diffusion tensor imaging (DTI)/diffusion kurtosis imaging (DKI) can only provide a composite view of the complex neuronal tissue, multicompartiment models, such as neurite orientation dispersion and density imaging (NODDI), provide an alternative representation that may enable investigation of the contributing tissue components individually. FW, free water. Microstructure Imaging Group - University College London. NODDI Matlab Toolbox. Available at: <http://mig.cs.ucl.ac.uk/index.php?n=Tutorial.NODDI matlab>. Accessed November 20, 2021.

deviating from the true underlying value. The results show that if the true value is lower (higher) than the fixed diffusivity ($1.7 \mu\text{m}^2/\text{ms}$) by $0.1 \mu\text{m}^2/\text{ms}$, NDI is estimated to be 0.025 lower (higher), FWF to be 0.01 higher (lower), and ODI with negligible changes. Given that no histological technique currently exists to estimate true diffusivity, NODDI has chosen to assume a fixed diffusivity so that it can robustly estimate parameters that we can validate histologically, such as NDI and ODI. It is conceivable that the assumption of a common fixed diffusivity may not be valid at least in some circumstances. However, any evidence that supports this will have to come from the observed NDI and ODI deviation from their histological counterparts, but such histological evidence has yet to emerge.

The other parameter not explicitly shown in Figure 3 is ODI, which describes how widely the orientations of the neurites spread out in space. This is the third and final key metric provided by the NODDI model. The extraneurite compartment models the space outside the neurites. This compartment, modeled as a diffusion tensor, has two parameters: d_{\parallel} , the parallel diffusivity, and d_{\perp} , the perpendicular diffusivity. They are determined in terms of d_{in} , NDI, and ODI; see the original NODDI paper for details (13). Together with the intraneurite compartment, the two combine to describe the tissue space. While most contemporaneous multicompartiment models stop here, as noted earlier, NODDI explicitly accounts for CSF

contamination with the free water compartment. This compartment is modeled as an isotropic diffusion tensor with a diffusivity (d_{fw}) set to $3 \mu\text{m}^2/\text{ms}$, which is the diffusivity of free water at body temperature. Figure 4 illustrates the definition of the three NODDI metrics (FWF, NDI, and ODI) and the spatial maps of these metrics of a healthy volunteer compared with standard DTI metrics (fractional anisotropy and mean diffusivity).

Acquisition Parameters. NODDI makes use of standard diffusion-weighted MRI sequences based on so-called pulsed gradient spin-echo echo-planar imaging, which images the brain, a three-dimensional object, as a set of consecutive two-dimensional axial slices. The key acquisition factors to consider are acquisition time, spatial resolution, and microstructural resolution. The challenge is to design an imaging protocol with spatial and microstructural resolutions as high as possible while keeping the acquisition time at a minimum. See the Supplement for a detailed discussion.

Optimization for Tissue Class. A recent study (24) demonstrated that the default choice of d_{in} , which was estimated from the corpus callosum (23), is suitable for white matter but not optimized for gray matter. The study has shown that for gray matter, the optimal choice is about $1.1 \mu\text{m}^2/\text{ms}$.

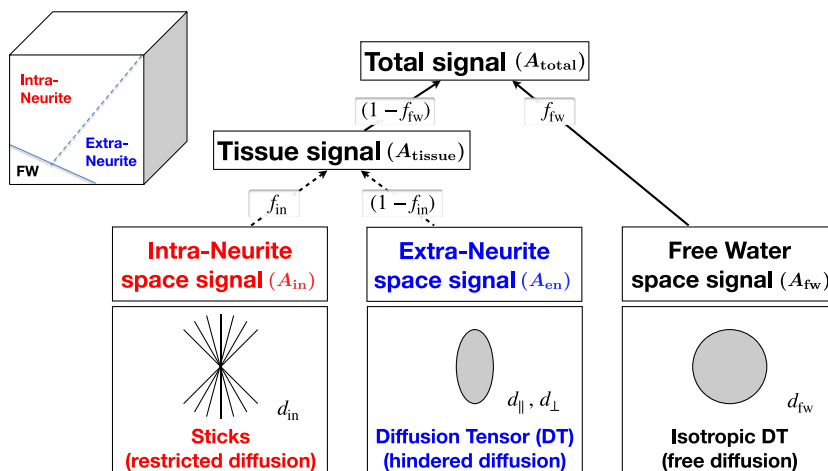


Figure 3. The detailed modeling behind neurite orientation dispersion and density imaging (NODDI). The observed signal at a voxel (A_{total}) is explained by the contribution from the constituting compartments, as well as how each compartment is modeled. See the text for full description. d_{\parallel} , parallel diffusivity; d_{\perp} , perpendicular diffusivity; d_{in} , rate of diffusion along individual neurites; f_{fw} , free water fraction; f_{in} , neurite density index. Microstructure Imaging Group - University College London. NODDI Matlab Toolbox. Available at: <http://mig.cs.ucl.ac.uk/index.php?n=Tutorial.NODDI matlab>. Accessed November 20, 2021.

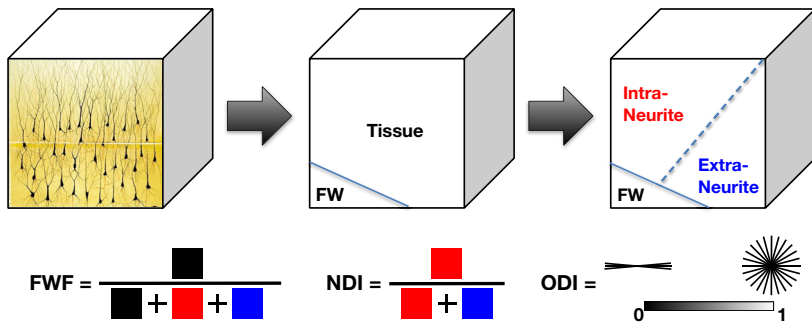
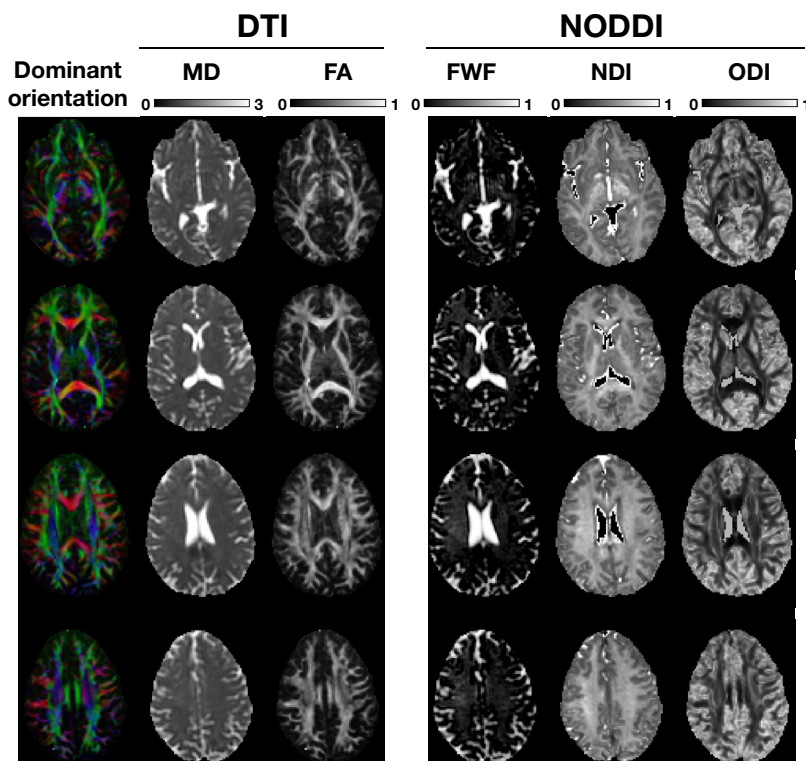


Figure 4. Schematic illustration of the three neurite orientation dispersion and density imaging (NODDI) metrics. Example maps of these metrics alongside those of the standard diffusion tensor imaging (DTI) metrics are provided for comparison. FA, fractional anisotropy; FW, free water; FWF, free water fraction; MD, mean diffusivity; NDI, neurite density index; ODI, orientation dispersion index. Microstructure Imaging Group - University College London. NODDI Matlab Toolbox. Available at: <http://mig.cs.ucl.ac.uk/index.php?n=Tutorial.NODDI matlab>. Accessed November 20, 2021.



Limitations. Model-based approaches, such as NODDI, enable researchers to make more direct inference on microstructural features using indirect MRI measurements. Modeling assumptions are an essential part of this type of approach. Constrained by the limited information content available from typical diffusion MRI acquisitions described earlier, different multicompartments models make different trade-offs in microstructural features they can estimate. For example, by including one more compartment than most of its contemporaneous models, NODDI gains the advantage of being able to quantify free water contamination that the other models cannot. However, this choice makes it necessary to forego the ability to estimate diffusivity parameters, such as d_{in} . As a result, NODDI must estimate this quantity a priori. In the original

implementation of NODDI, this quantity was estimated from the corpus callosum and assumed to be suitable for both white matter and gray matter. However, later it was shown that the appropriate value for gray matter is substantially different from the default (24). Moreover, while the appropriate d_{in} for different age groups is broadly similar across the lifespan (>10 years old), the value for infants (<1 year old) is substantially different. Another assumption that has been queried in the literature concerns d_{\perp} , the perpendicular diffusivity of the extraneurite space. In NODDI, this value is constrained to be proportional to $(1 - f_{in})$, based on the intuition that the extraneurite space is going to be reduced if f_{in} is increased. Because this leads to a more congested extraneurite space for water molecules to diffuse, NODDI assumes that this translates into reduced d_{\perp} .

Lampinen *et al.* (25) have shown that NODDI is incompatible with a new class of diffusion MRI data acquired with b-tensor encoding and suggested that this constraint is the source of the incompatibility. However, Guerrieri *et al.* (26) later demonstrated that this conclusion is unjustified and the primary source of the incompatibility is in fact d_{in} being chosen inappropriately, requiring tissue-specific optimization. Despite these limitations, NODDI is one of the few multicompartment models that have been extensively histologically validated (14–18).

Systematic Review of Applications of NODDI in Psychiatric Disorders

Study Identification and Characteristics. We identified a total of 18 articles that met the inclusion criteria (Figure 1). Seven studies assessed microstructure in psychosis spectrum disorders, four in mood disorders (one assessed both patients with bipolar disorder and with schizophrenia), five in neurodevelopmental and other disorders of childhood and adolescence, and one study each examined NODDI indices in binge drinking, chronic fatigue syndrome, and psychogenic non-epileptic seizures (Table 1).

Findings From NODDI Studies in Psychiatric Disorders: Psychosis Spectrum Disorders.

In psychosis spectrum disorders, all but one study (27) report altered brain microstructure in patients compared with control subjects. One study in antipsychotic medication-naïve patients with first-episode psychosis found that NDI is altered in many white matter tracts and differentially expressed depending on the fiber type (increased in projection fibers, decreased in commissural and association fibers), while an increase in ODI was widespread (28). Greater microstructural abnormalities were associated with a longer duration of untreated psychosis, an environmental factor that affects long-term outcomes, supporting the idea that the duration of untreated psychosis may have fundamental pathogenic effects (28). In medicated first-episode patients, a widespread decrease in white matter NDI without corresponding ODI change was reported (29). Interestingly, the authors did report a relationship between age and changes in fiber organization in patients but not in control subjects, suggestive of white matter disease progression. The two studies in first-episode patients are similar as they both detected NDI reductions in patients in association fibers, but only the first study described increased NDI in projection fibers and abnormalities in ODI. It is unclear if the discrepancies in findings are in fact due to medication exposure or to what extent differences in data acquisition (magnetic field strength and image resolution were higher in the first study) and analysis approaches (voxel-based morphometry and tract-based spatial statistics, respectively) or patient characteristics account for the variability in results. Gray matter microstructural abnormalities were assessed in three studies of patients with chronic psychosis spectrum disorders (30–32). Findings are mixed, where decreased NDI was reported in the temporal lobe (30) and frontotemporal regions (31), whereas ODI was reported to be decreased in the anterior cingulate cortex and medial frontal gyrus (32) and increased in the posterior cingulate cortex and supplemental motor area (30). While some did not report associations between brain microstructure and

clinical variables (29,31), many did find relationships with clinical variables. In a cross-sectional study in medicated patients with first-episode psychosis, NDI in the hippocampus was correlated with metacognitive accuracy (27), where poorer metacognitive accuracy corresponded with lower NDI, which is consistent with reported reductions of dendritic density in the subiculum in postmortem studies and highlights the importance of microstructure in hippocampus neurocircuitry. Similarly, Nazeri *et al.* (30) found that gray matter NDI is relevant for cognition in patients with chronic schizophrenia. They report that higher NDI in the medial and dorsolateral prefrontal, superior temporal, and cingulate cortices, as well as the insula, striatum, and hippocampus was associated with better performance in spatial working memory (30). A longitudinal study examining effects of risperidone on white matter microstructure found that baseline ODI in unmedicated patients with psychosis spectrum disorders was predictive of subsequent treatment response, where higher whole-brain white matter ODI predicted worse clinical outcomes (33).

Findings From NODDI Studies in Psychiatric Disorders: Mood Disorders.

In bipolar disorder, one study found reductions in white matter NDI and ODI in posterior cingulate regions and the hippocampus, respectively (34). A small multicenter study used a cross-sectional design and reported reduced frontal gray matter NDI in patients who were not treated with lithium but not in those who were treated with lithium (35). This provides preliminary evidence suggesting that lithium may normalize white matter microstructure, although this is in need of replication in a well-powered longitudinal study. Neither of these studies detected associations between brain microstructure and clinical variables. The only study conducted in major depressive disorder reported reduced NDI in the inferior frontal cortex, insula, parahippocampus, superior temporal cortex, and cerebellum. In contrast, ODI was reduced in the thalamus and occipital gyrus and increased in the posterior thalamic radiation and superior longitudinal fasciculi (36). In this study, only ODI in the inferior frontal and middle frontal gyri was positively correlated with depressive symptom severity.

Findings From NODDI Studies in Psychiatric Disorders: Neurodevelopmental and Other Disorders of Childhood and Adolescence.

Three studies assessed NODDI indices in patients with autism spectrum disorder (37–39). One study investigated gray matter microstructure and found increased ODI in the left occipital gyrus. ODI in this region was also correlated with resting-state functional connectivity between the occipital gyrus and medial temporal gyrus and associated with atypical visual processing in patients (38). Another study in young and middle-aged adults with autism spectrum disorder examined microstructure in white matter and found widespread reductions in NDI and increases in FWF but no abnormalities in ODI (39), consistent with postmortem studies reporting reduced numbers of medium- and large-caliber axons (40,41). In patients, NDI in the anterior thalamic radiation, superior longitudinal fasciculus, and uncinate fasciculus, which are language-related and social processing-related white matter tracts, was negatively

Table 1. Articles Included in Systematic Review of NODDI Studies in Psychiatry

Author, Year	Disorder	Illness Duration	Medication Status	HC/ Pt, n	Age, Years	% Male	T	Acquisition Parameters	NODDI Indices Modeled	Analysis Method	Region of Interest	Findings in Patients Compared With Control Subjects	Associations With Clinical Variables
Hanlon <i>et al.</i> , 2021 (31)	Psychosis spectrum disorder	Chronic	Medicated	63/150	HC: 33.3 ± 8.3 Pt: 32.0 ± 9.4	HC: 65.1 Pt: 60.7	3	87 directions b = 800, 1600, 2400	NDI, FWF	VBM	GM, WM	↓NDI in the lateral prefrontal cortex, superior/medial frontal gyrus, central sulci, superior temporal gyrus, and middle temporal gyrus ↓FWF in the SLF ↑FWF in the cerebral and cerebellar peduncle	None
Kraguljac <i>et al.</i> , 2021 (55)	Psychosis spectrum disorder	First episode	Medication naïve	64/78	HC: 24.3 ± 5.9 Pt: 23.7 ± 6.0	HC: 64.1 Pt: 64.1	3	98 directions b = 1500, 3000	NDI, ODI, FWF	VBM	WM	↓NDI in commissural and association fibers ↑NDI in projection fibers ↑ODI widespread ↑↓ FWF across regions	Greater duration of untreated psychosis is associated greater abnormalities in all NODDI indices
Alkan <i>et al.</i> , 2020 (27)	Psychosis spectrum disorder	First episode	Medicated	18/31	HC: 24.1 ± 4.9 Pt: 26.2 ± 5.7	HC: 72.2 Pt: 76.3	1.5	9, 30, 60 directions b = 300, 800, 2400	NDI, ODI	ROI	Hippocampus	No group differences in NDI or ODI	NDI in the hippocampus correlates with metacognitive accuracy
Kraguljac <i>et al.</i> , 2019 (33)	Psychosis spectrum disorder	First episode, chronic	Unmedicated	42/42	HC: 27.9 ± 9.4 Pt: 26.6 ± 9.0	HC: 61.9 Pt: 61.9	3	30 directions b = 1000	ODI, FWF	VBM	WM	↑ODI in the posterior limb of the IC	ODI is negatively correlated with subsequent antipsychotic treatment response
Rae <i>et al.</i> , 2017 (29)	Psychosis spectrum disorder	First episode	Mixed	19/35	HC: 24.7 Pt: 26.9	HC: 68.4 Pt: 77.1	1.5	9, 30, 60 directions b = 300, 800, 2400	NDI, ODI	TBSS	WM	↓NDI in many white matter tracts No ODI abnormalities	None
Parvathaneni <i>et al.</i> , 2017 (32)	Psychosis spectrum disorder	NR	NR	47/67	NR	NR	3	24, 60 directions b = 1000, 2000	V _{IC} , V _{ISO} , ODI	GS-BSS	GM	↓ODI in the anterior cingulate cortex and medial frontal gyrus	NR
Nazeri <i>et al.</i> , 2017 (30)	SZ, BD	Chronic	Medicated	35/65	HC: 33.6 ± 12.4 SZ: 35.5 ± 8.4 BD: 31.5 ± 11	HC: 54.3 SZ: 52.8 BD: 48.3	3	30, 30, 30 directions b = 1000, 3000, 4500	NDI, ODI	GS-BSS	GM	↓NDI in the rostromedial temporal lobe in SZ ↑ODI in the PCC SMA and lateral occipital cortex in SZ No alterations in BD	Higher NDI in frontotemporal areas was correlated with better spatial span performance

Table 1. Continued

Author, Year	Disorder	Illness Duration	Medication Status	HC/Pt, n	Age, Years	% Male	T	Acquisition Parameters	NODDI Indices Modeled	Analysis Method	Region of Interest	Findings in Patients Compared With Control Subjects	Associations With Clinical Variables
Sarrazin <i>et al.</i> , 2019 (35)	BD	Chronic	Medicated	40/41	HC: 36.1 ± 10.1 BD/+Li: 37.1 ± 13.8 BD/-Li: 42.3 ± 12.7	HC: 47.5 BD/+Li: 57.7 BD/-Li: 46.7	3	30, 60, 60 directions b = 200, 1500, 2700	NDI	ROI	GM	↓NDI in patients not on Li but not in patients on Li	NDI was not correlated with Li dose or serum level in patients
Ota <i>et al.</i> , 2019 (34)	BD	Chronic	Medicated	28/31	HC: 42.3 ± 12.6 Pt: 39.5 ± 9.3	HC: 39.3 Pt: 45.2	3	16 directions b = 1000, 2000	NDI, ODI	VBM	WM	↓NDI in the PCC ↓ODI in the hippocampus	None
Ota <i>et al.</i> , 2018 (36)	MDD	Chronic	Medicated	26/23	HC: 42.9 ± 12.9 Pt: 42.3 ± 13.4	HC: 42.3 Pt: 39.1	3	16 directions b = 1000, 2000	NDI, ODI	VBM	GM, WM ROI in CC, IC, SLF, and posterior thalamic radiation	↓NDI in the inferior frontal cortex, insula, parahippocampus, superior temporal cortex, cerebellum ↓ODI in the thalamus and occipital gyrus ↑ODI in the SLF, posterior thalamic radiation, and parietal cortex	ODI in the inferior frontal and middle frontal gyrus was correlated with depression severity
Morris <i>et al.</i> , 2018 (47)	Binge drinking	NR	NR	38/28	HC: 23.7 ± 3.9 Pt: 22.0 ± 4.5	HC: 36.8 Pt: 60.7	3	33, 65 directions b = 700, 2850	NDI, ODI	VBM, ROI	GM, WM, ventral striatum	↑NDI in the superior and middle frontal gyrus, inferior parietal cortex ↓NDI in the postcentral gyrus, angular gyrus, MOG ↓ODI in the DLPFC, inferior parietal cortex, and MOG ↑ODI in the angular and supramarginal gyri, ventral striatum	ODI in the striatum was correlated with binge drinking scores
Kimura <i>et al.</i> , 2019 (46)	Chronic fatigue syndrome	Chronic	NR	23/20	HC: 38.2 ± 9.2 Pt: 39.8 ± 8.2	HC: 4.4 Pt: 5.0	3	32 directions b = 1000, 2000	NDI, ODI	VBM	WM	↓NDI in the PCC and SLF ↓ODI in occipital areas, putamen, and PCC ↑ODI in occipital and temporal areas	NR

Table 1. Continued

Author, Year	Disorder	Illness Duration	Medication Status	HC/ Pt, n	Age, Years	% Male	T	Acquisition Parameters	NODDI Indices Modeled	Analysis Method	Region of Interest	Findings in Patients Compared With Control Subjects	Associations With Clinical Variables
Goodman <i>et al.</i> , 2020 (44)	Psychogenic nonepileptic seizures	NR	NR	37/34 ^a	CG ^a : 39.7 ± 10.9 Pt: 36.7 ± 11.8	CG ^a : 56.8 Pt: 29.4	3	47, 46 directions b = 1500, 3000	ODI, NDI, FWF	VBM	WM	↓NDI in the UF, corticospinal tract, and cingulum pathways ↓FWF in the corticospinal tract	ICVF in the corticospinal tract and posterior cingulum were negatively correlated with depression FWF in the corticospinal tract was negatively correlated with posttraumatic stress scores
Andica <i>et al.</i> , 2021 (39)	ASD	Chronic	NR	25/26	HC: 34.4 ± 9.0 Pt: 32.9 ± 9.2	HC: 68.0 Pt: 73.1	3	32 directions b = 1000, 2000	NDI, ODI, V _{iso}	TBSS, ROI	WM	↓NDI in the right hemisphere and anterior left hemisphere ↑V _{iso} in the posterior left hemisphere	NDI in the ATR was negatively correlated with communication scores
Matsuoka <i>et al.</i> , 2020 (38)	ASD	Chronic	Mixed	29/28	HC: 27.3 ± 4.9 Pt: 28.9 ± 6.0	HC: 82.8 Pt: 85.7	3	30, 30 directions b = 1000, 2000	NDI, ODI	VBM	GM	↑ODI in the occipital gyrus	ODI was positively correlated with low registration and a passive behavioral response
Yasuno <i>et al.</i> , 2020 (37)	ASD	Chronic	Mixed	27/18	HC: 25.5 ± 2.7 Pt: 28.9 ± 8.2	HC: 92.6 Pt: 88.9	3	30, 30 directions b = 1000, 2000	NDI, ODI	VBM	GM, WM	No group differences	NDI in the fusiform and inferior parietal gyrus and CC and ODI in the ventral occipital and superior temporal regions was negatively correlated with recognition
Caverzasi <i>et al.</i> , 2018 (42)	Developmental dyslexia	NR	NR	56/39	HC: 10.0 ± 1.8 Pt: 10.0 ± 1.9	HC: 57.1 Pt: 50.0	3	30, 64 directions b = 700, 2000	NDI, ODI	ROI	GM	Abnormal interaction between NODDI and gyrification	NR
Sun <i>et al.</i> , 2020 (43)	Primary nocturnal enuresis	Chronic	NR	34/29	HC: 10.3 ± 1.6 Pt: 9.8 ± 1.2	HC: 56.0 Pt: 59.0	3	32 directions b = 700, 2000	NDI, ODI	TBSS	WM	↓NDI in the IC and cingulum ↑NDI in the SLF ↓ODI in the SLF ↑ODI in the IC and ATR	NDI in the ATR was negatively correlated with arousal from sleep score in patients

ASD, autism spectrum disorder; ATR, anterior thalamic radiation; BD, bipolar disorder; CC, corpus callosum; CG, control group; DLPFC, dorsolateral prefrontal cortex; FWF, free water fraction; GM, gray matter; GS-BSS, gray matter surface-based spatial statistics; HC, healthy control; IC, internal capsule; ICVF, intracellular volume fraction; Li, lithium; MDD, major depressive disorder; MOG, middle occipital gyrus; NDI, neurite density index; NODDI, neurite orientation dispersion and density imaging; NR, not reported; ODI, orientation dispersion index; PCC, posterior cingulate cortex; Pt, patient; ROI, region of interest; SLF, superior longitudinal fasciculus; SMA, supplemental motor area; SZ, schizophrenia; T, tesla; TBSS, tract-based spatial statistics; UF, uncinate fasciculus; VBM, voxel-based morphometry; WM, white matter.

^aClinical control group.

correlated with communication scores, where deficits in communication are at the core of this illness. The third study failed to detect abnormalities in NDI and ODI in either gray matter or white matter (37). When the patient group was divided into those with greater and lesser impairments in recognition of facial emotional expressions, both NDI and ODI differed between subgroups. Taken together, all studies in autism spectrum disorder have discovered microstructural features that demonstrate clinical relevance.

Two studies investigated other psychiatric disorders of childhood and adolescence. In developmental dyslexia, Caverzasi *et al.* (42) performed a multimodal imaging study assessing local gyrification, NDI, and ODI in regions of the language network. While they did not directly contrast microstructure indices between patients and typically developing control subjects, they examined the relationships between local gyrification and NODDI metrics and found an interaction between gyrification and ODI in the middle frontal gyrus and NDI in the medial temporal gyrus, suggesting a relationship between cortical morphology and microstructural organization. Another study examined white matter microstructure in children with primary nocturnal enuresis (43) and found a mixed picture of NDI increase (superior longitudinal fasciculus) and decrease (internal capsule and cingulum) as well as ODI increase (internal capsule and anterior thalamic radiation) and decrease (superior longitudinal fasciculus) in patients. NDI in the anterior thalamic radiation showed a negative correlation with sleep arousal scores in patients, suggesting that altered microstructure may result in the inability to wake up from sleep in response to the need to urinate.

Findings From NODDI Studies in Psychiatric Disorders: Psychiatric Disorders With Somatic Manifestations. Goodman *et al.* (44) examined white matter microstructure using NODDI in patients with psychogenic nonepileptic seizures. Notably, both the patient and control groups also carried a diagnosis of traumatic brain injury, a common comorbidity (45). They found decreased NDI in the fornix, uncinate fasciculus, cingulum, and corticospinal tract in patients with psychogenic nonepileptic seizures compared with those without. In addition, FWF in the corticospinal tract was lower in this group and associated with severity of post-traumatic stress symptoms. While this study suggests microstructural involvement in psychogenic nonepileptic seizures, due to the lack of inclusion of a control group, it is difficult to interpret data with respect to directionality of abnormalities.

In chronic fatigue syndrome, NDI was found to be decreased in the posterior cingulate cortex, superior longitudinal fasciculus, and frontal white matter. ODI showed a mixed picture of decrease in the posterior cingulate cortex, superior temporal gyrus, and putamen and increase in temporal and occipital areas (46). No associations with clinical or behavioral variables were tested in this study.

Findings From NODDI Studies in Psychiatric Disorders: Substance Use Disorders. In a study contrasting patients with binge drinking behaviors and healthy control subjects, Morris *et al.* (47) found reduced ODI in frontal cortical gray matter and increased ODI in the parietal cortex. NDI was

increased in cortical white matter in regions adjacent to those with lower ODI. While alcohol use severity or binge drinking patterns were not related to overall microstructural changes, higher ODI in the ventral striatum, a key region of the reward system, was associated with binge severity in binge drinking, suggesting a role of ventral striatal neurite integrity in the pathophysiology.

DISCUSSION

We performed a systematic review of the emerging NODDI literature in psychiatric disorders. Consistent with postmortem and neuroimaging studies that have implicated microstructural involvement in virtually all major psychiatric disorders, a general theme of abnormal gray and white matter microstructure in patients with psychiatric disorders emerged. However, findings within and across diagnostic groups were variable, both in terms of spatial patterns of microstructure abnormalities and in the directionality of alterations. In addition, we noted associations between brain microstructure and phenotypical variables, suggesting that NODDI may provide useful information in detecting clinically relevant brain signatures.

Our review highlights the increasing popularity of advanced diffusion imaging as a tool to characterize brain microstructure alterations in psychiatric disorders. This is perhaps not surprising because it holds promise to improve sensitivity to target pathologies and provide better explanations for observed abnormalities compared with traditional DTI (48). All but two studies included in our systematic review detected abnormalities in NODDI metrics in patients, and many also reported associations with clinical variables, providing proof-of-concept for detecting microstructural properties affected in psychiatric disorders (49). We also noted that findings were variable across studies within the same diagnostic group. It is an open question as to what extent this variability is a reflection of the known pathophysiological heterogeneity underlying psychiatric syndromes, the stage of the illness, or other factors such as medication effects. In addition, many of the studies did not use sequence parameters optimized for NODDI, and model parameters were typically not adjusted for tissue type, which may be a function of the relative novelty of the method. Nonetheless, NODDI is fairly robust to the choice of acquisitions; see the [Supplement](#) for details. Nevertheless, findings in psychiatric disorders to date have to be interpreted with caution, pending larger-scale replications with optimized sequence and model parameters.

To date, NODDI has been implemented in cross-sectional designs with the goal to describe microstructural abnormalities in psychiatric disorders, but there are countless opportunities for implementation of this method in studies geared at elucidating pathophysiological mechanisms, biomarker development, and clinical translation. For example, prospective studies could uncover microstructure abnormalities in at-risk patients that predispose them to developing a psychiatric condition in the future or detect abnormalities in early illness patients that prove useful in predicting the eventual clinical course. The method also lends itself well to longitudinal studies (50,51) because repeatability of NODDI is excellent, with intrasubject coefficients of variations for NDI and ODI mostly below 5% (48). This type of design is ideal for studying

effects of psychotropic medications on brain microstructure and investigating the interplay between brain microstructure changes and disease progression. Finally, it could be used in multimodal studies designed to elucidate complex disease mechanisms. For example, it is not yet known if NDI or ODI abnormalities have functional consequences in psychiatric disorders, e.g., do these alterations affect connectivity or synchrony of large-scale functional brain networks, or can variance in functional network abnormalities be attributed to these microstructure deficits? Similarly, the field has only begun to study how genes, specifically those that are linked to brain development and plasticity, may be related to brain microstructure in general and NODDI indices specifically (52), and only one study has examined the impact of risk genes for psychiatric disorders on NDI and ODI (53), which could elucidate mechanistic aspects of observed microstructure alterations.

Of course, several limitations have to be discussed. While NODDI aims to provide a better characterization of microstructure tissue properties and histological evidence suggests that NDI and ODI reasonably represent histology-based neurite density and orientation dispersion, it is critical to be mindful of the model limitations when it comes to making inferences on a biological level. For example, NODDI may be sensitive to a change in neurite spine density, but we will unlikely be able to attribute any changes to NODDI metrics to a change in neurite spine density specifically. For the latter, more complex models will be required. However, estimating parameters from such models may not be possible from the data we can acquire routinely today. For example, soma and neurite density imaging is a recently developed technique that can additionally estimate soma density, but it requires data that currently can only be acquired with the Siemens Connectom scanner; there are only four such scanners in the world (54). In contrast, in the context of clinical applications, the ability to use these quantitative metrics for diagnostic and predictive processes would supersede necessity for histological accuracy. The current NODDI literature, while growing, is limited, and only approximately 60% of published papers (30,34–39,43,46,47) included means and standard deviations of indices or a full list of clusters (cluster extent, coordinates, *t* statistics) with diffusion abnormalities, which prevented us from quantitatively reviewing findings with meta-analytic approaches. It will be helpful for future publications to include comprehensive summary statistics of NODDI abnormalities, which will enable coordinate-based meta-analyses. Most, but not all, studies have accounted for age (27), sex (44), or both (29,30,33–39,43,46,47,55) in their statistical models. Population and lifespan trajectory studies have demonstrated that NODDI metrics are sensitive to development and aging effects (56–58) and sex differences (59), underscoring the importance to account for these variables when studying psychiatric disorders. However, there are not sufficient data available to determine the presence or extent of sex differences in abnormal NODDI signatures in psychiatric disorders. Finally, many of the studies did not adjust (or did not report that they adjusted) model parameters for tissue type, which could bias findings, especially in studies assessing gray matter microstructure. Moving forward, it will be important to account for tissue type when assessing microstructure abnormalities and include model parameters as a standard for reporting to maximize transparency.

In summary, our review summarizes proof-of-concept that NODDI can be successfully used to detect subtle microstructure abnormalities in patients with psychiatric disorders. However, even though the number of studies is growing, the body of literature for most disorders remains small, and we have very little knowledge on the effects of medication, illness duration, clinical subtypes, or association with symptom domains and other behavioral measures relevant to psychiatric disorders. More data are needed to begin to fill these gaps in the literature. Given that NODDI indices may provide a more direct link to pathophysiological processes compared with the traditional tensor model, this method may not only contribute to advancing our mechanistic understanding of disease processes, it may also be well positioned for next-generation biomarker development studies (60).

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