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REVIEW ARTICLE

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Cortical complexity estimation using fractal dimension: A systematic review of the literature on clinical and nonclinical samples

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Abstract

Fractal geometry has recently been proposed as a useful tool for characterizing the complexity of the brain cortex, which is likely to derive from the recurrence of sulci–gyri convolution patterns. The index used to describe the cortical complexity is called fractal dimensional (FD) and was employed by different research exploring the neurobiological correlates of distinct pathological and nonpathological conditions. This review aims to describe the literature on the application of this index, summarize the heterogeneities between studies and inform future research on this topic. Sixty-two studies were included in the systematic review. The main research lines concern neurodevelopment, aging and the neurobiology of specific psychiatric and neurological disorders. Overall, the included papers indicate that cortical complexity is likely to reduce during aging and in various pathological processes affecting the brain. Nevertheless, the high heterogeneity between studies strongly prevents the possibility of drawing conclusions. Further research considering this index besides other morphological values is needed to better clarify the role of FD in characterizing the cortical structure.

KEYWORDS
cortical complexity, cortical structure, fractal dimension, MRI

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AN, anorexia nervosa; ASD, autism spectrum disorder; BMI, body mass index; BN, bulimia nervosa; CSF, cerebrospinal fluid; DLPFC, dorsolateral prefrontal cortex; FA, folding area; FD, fractal dimension; FLE, frontal lobe epilepsy; FTD, frontotemporal dementia; GI, gyrification index; GM, grey matter; HC, healthy control; ICC, intraclass correlation; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; MS, multiple sclerosis; NSCLP, non-syndromic lip and palate cleft; OCD, obsessive–compulsive disorder; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRS, polygenic risk scores; SCA, spinocerebellar ataxia; SVD, small vessel disease; TLE, temporal lobe epilepsy; WM, white matter.

Valentina Meregalli and Francesco Alberti equally contributed to this paper.

1 | INTRODUCTION

In recent decades, the study of the cerebral cortex has benefited from the introduction of increasingly refined and complex computational methods, which have allowed characterizing its structure within different frameworks that are both physiological (neurodevelopment and aging) and pathological (neurological and psychiatric conditions). Difficulties in the quantitative characterization of the cortex are mainly due to its morphological complexity, which arises from its convoluted structure (Hofman, 1991). Surface-based morphometry techniques have been shown to be particularly useful in this context, as they allowed the description of parameters that characterize specific aspects of the cortex, such as its thickness, gyrification index (GI), sulcal width and depth (Collantoni et al., 2021; Dale et al., 1999; Fischl & Dale, 2000; Madan, 2019; Schaer et al., 2008). The usefulness of using different indices to quantitatively characterize the cortex is mainly due to their ability to offer a nonredundant description of structural features that vary differently during development and aging and that are differently affected by distinct pathological processes (Im et al., 2006; King et al., 2010; Madan & Kensinger, 2016). To improve the understanding of the neurobiological mechanisms underlying different brain disorders, development and aging, important efforts have been made in recent years to find novel methodological tools to complement existing ones. In this regard, one of the most promising indices is the fractal dimension (FD), a measure that has long been used to describe the complexity of many 'natural' structures (Mandelbrot, 1967) and which has been applied to evaluate the complexity of the brain across multiple scales, from molecular to whole brain (Di Ieva et al., 2014, 2015). FD is an index that summarizes the morphological detail of an object in a range of spatial scales, providing a numerical value of the self-similarity of a structure or, more in general, its overall complexity. Grey matter (GM) can be examined through fractal geometry tools because of the fractal properties of its complex geometry, which result from the recurrence of convolution patterns. This complexity arises from the contribution of different GM components, which are the pial surface, the GM–white matter (WM) interface and the cortical ribbon (Esteban et al., 2009; Goñi et al., 2013; Im et al., 2006; Madan & Kensinger, 2016). Different FD calculation methodologies may or may not consider all these different aspects, thus guiding the interpretation of the data towards some cortical features rather than others. The procedure most commonly applied to compute the FD of the cortex is the box-counting algorithm, which is designed to estimate the space-filling property of an object regardless of whether it is a fractal or not. This method can be applied in a 2D and a 3D implementation to brain slices and volume or surface, respectively. In both cases, the brain object is iteratively enclosed in two- or three-dimensional grids of decreasing box size. The FD is, then, estimated as the slope of the regression line for the logarithm of the number of boxes needed to cover the object versus the logarithm of the grid scale. At present, different toolboxes based on the box-counting approach have been proposed and applied in the neuroscientific field (Madan & Kensinger, 2016). Nevertheless, other ways to characterize cortical complexity through FD also exist, such as methods based on fast Fourier transform, surface dilation and spherical harmonic reconstructions (Kiselev et al., 2003; Yotter et al., 2011). All these procedures can be applied to surface objects—for example, the pial surface or the interface between WM and GM—but only the first three can also estimate the FD of brain volumes—for example, the cortical ribbon (Free et al., 1996).

The presence of different computational tools for estimating FD which have been applied to heterogeneous experimental samples with respect to age, development stage, clinical situation and so on make the literature on this field extremely varied. In general, this research analyses how cortical complexity changes during development and aging in nonpathological contexts (Blanton et al., 2001; Kalmanti & Maris, 2007; Madan & Kensinger, 2016). In this regard, attempts to clarify how much FD is related to other indices such as thickness and gyrification are particularly interesting in demonstrating how this measure can provide novel insights into cortical architectural features (King et al., 2009, 2010). Other lines of research involve studies aimed at assessing cortical complexity in samples of patients with neurological or psychiatric disorders by comparing FD values with healthy control (HC) samples and testing possible associations with clinical data (Collantoni et al., 2020; King et al., 2010). In this regard, it should be noted that a proper interpretation of the FD data obtained from clinical populations cannot ignore those obtained from healthy samples, because the neurobiology of brain disorders is largely motivated by neurodevelopmental alterations and atrophic/neurodegenerative phenomena (Thibaut, 2018). This review aims to summarize the current literature on the application of FD to describe cortical complexity in healthy and clinical populations, including studies assessing the accuracy and reliability of the estimation procedures. We also aim to identify the main points of variation between studies and to inform future research on this topic.

2 | MATERIALS AND METHODS

2.1 | Literature search

The literature search for this paper was performed on 23 March 2021, relying on two separate digital archives—that is, PubMed (pubmed.ncbi.nlm.nih.gov) and SCOPUS (www.scopus.com). The key used for both search engines was *((cortical complexity) OR (fractal dimension) OR (FD)) AND ((MRI) OR (neuroimaging) OR (imaging)) AND ((cortex) OR (cortical structure))*. We searched for a combination of these terms in the titles, abstracts and keywords of all articles available in the two archives, from inception to the present. It should be taken into consideration that this procedure may have introduced a bias against those studies that did not use these terms in their title, abstract or keywords (e.g., studies that only refer to this measure with other expressions, such as cortical complexity).

The review was carried out according to the statement Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021), following an a priori protocol (https://mfr.osf.io/render?url=https%3A%2F%2Fosf.io%2F7hbtj%2Fdownload).

2.2 | Study selection

A first screening of the search output was independently carried out by two authors (VM and FA) based on the articles' titles first and then on their abstracts. Any conflicts in the selection process were resolved with the contribution of a third author (EC).

Following the screening, we proceeded to assess the remaining articles in full text to identify the papers to be reviewed. At this stage, we decided to only include studies fulfilling the following criteria: (i) calculation of cerebral cortex FD with any of the existing methods, (ii) inclusion of a control group when studying specific clinical populations, (iii) publication in a peer-reviewed journal and (iv) written in English.

Additional articles were included by consulting the reference lists of the included papers and based on previous knowledge of the authors. Figure 1 describes the process of study selection.

2.3 | Data extraction and synthesis

Through the full-text review, we extracted the following information from all included articles (when possible): (i) characteristics and demographics of the participant samples (numerosity, age, sex and pathologies), (ii) features of image acquisition and processing (image resolution, processing software), (iii) algorithm used for the FD computation and (iv) main findings (including whole-brain FD values when available). This information is summarized in Table 1.

To synthesize the findings of the included articles, we divided them in six groups based on their object of investigation: reliability of FD estimation, comparison with other cortical measures, FD in healthy individuals, FD in

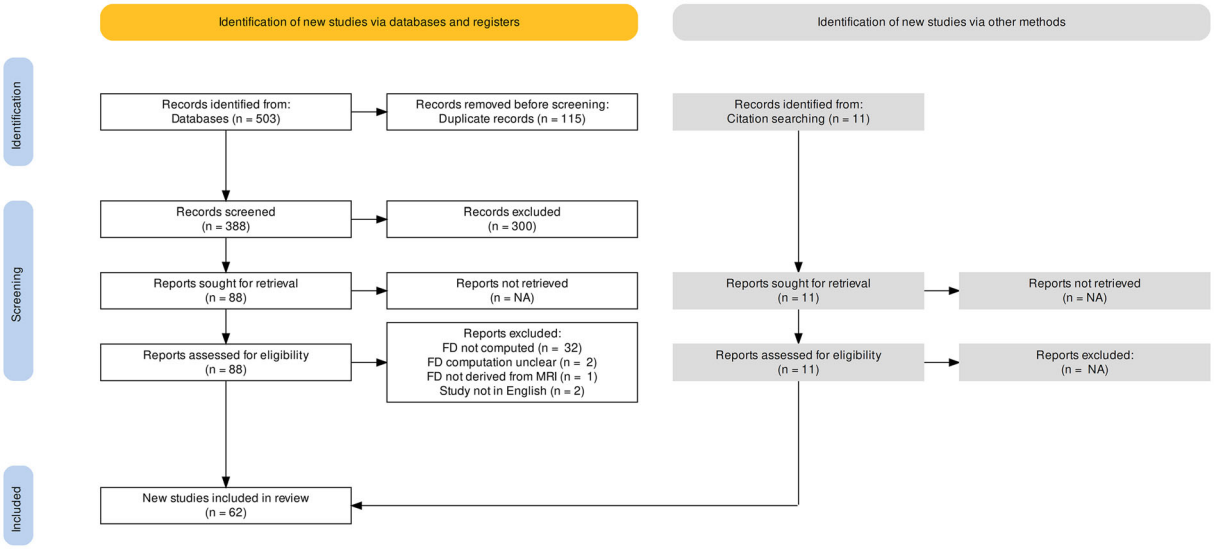

FIGURE 1 PRISMA flowchart

TABLE 1 Summary of the reviewed studies

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Blanton et al. (2001)	USA	Cross-sectional	Children (13) Adolescents (11)	54% 55%	9.3 (1.7) 13.3 (1.1)	1.5 T	Surface algorithm		Positive correlation between age and FD of the L and R inferior and L superior frontal regions ($p = .001$, $p < .001$, $p = .009$). Lower FD in children than in adolescent in L and R inferior frontal regions ($p = .001$, .007). Significant gender by age interaction in L superior and R inferior frontal regions with complexity only increasing in females with age ($p = .001$, $p = .007$).
Bullmore et al. (1994)	UK	Case–control	Schizophrenia (39) Bipolar disorder (23) HC (31)	Whole: 40%	Whole: ≤50	.5 T	2D box-counting (Analyze, custom script)	1.40 (.02) 1.41 (.02) 1.40 (.02)	Significant effect of diagnosis on FD ($p = .05$), no effect of sex. Higher FD in bipolar patients than in HC ($p = .04$). No difference in FD between schizophrenia patients and HC. Positive correlations between FD and WM volume, anterior cerebral volume and total intracranial volume. Negative correlations between FD and CSF volume and GM volume.

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Cascino et al. (2020)	Italy	Case–control	Anorexia nervosa (22) Recovered from AN (10) Bulimia nervosa (24) HC (35)	100% 100% 100% 100%	28.6 (9.8) 25.5 (6.7) 27.2 (7.1) 26.8 (5.2)	3.0 T	3D box-counting (FreeSurfer 5.3.0, calcFD)		No significant differences in FD between groups.
J. H. Chen, Huang, et al. (2020)	China	Case–control	Amyotrophic lateral sclerosis (22) HC (20)	32% 40%	57.2 (10.2) 54.5 (5.5)	3.0 T	Spherical harmonic reconstructions (SPM12, CAT12)		Lower FD in amyotrophic lateral sclerosis patients than in HC in L precentral gyrus and central sulcus; L circular sulcus of insula (superior segment); L cingulate gyrus and sulcus (middle-posterior part); R precentral gyrus; R postcentral gyrus. Negative correlations between disease severity and rate of disease progression and FD of the R precentral gyrus ($p = .023$). Negative correlation between disease duration and FD of the L circular sulcus of the insula (superior segment) ($p = .010$).
Q. F. Chen, Zhang, et al. (2020)	China	Case–control	Minimal hepatic encephalopathy (20) HC (21)	20% 29%	50.0 (8.2) 48.9 (10.9)	3.0 T	Spherical harmonic reconstructions (SPM12, CAT12)		Lower FD in minimal hepatic encephalopathy patients than in HC in L precuneus; L paracentral gyrus; supramarginal gyrus; pericalcarine cortex; caudal anterior cingulate cortex; isthmus cingulate cortex; insula cortex; paracentral cortex. Positive correlations between patients' cognitive performance and FD of the R isthmus cingulate ($p = .006$) and R insula ($p = .002$).

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Collantoni et al. (2020)	Italy	Case–control	Anorexia nervosa (38) Recovered from AN (20) HC (38)	100% 100% 100%	26.1 (7.2) 26.3 (7.0) 25.2 (6.7)	1.5 T	Dilation algorithm (FreeSurfer 5.3.0, calcFD)	2.49 (.02) 2.52 (.02) 2.51 (.01)	Lower FD in anorexia patients (AN) than in HC in 22 cortical areas, whole brain ($p < .001$), frontal lobe ($p = .001$), parietal lobe ($p < .001$), temporal lobe ($p = .023$) and occipital lobe ($p < .001$). No differences between restricting and binge purging type. Higher FD in recovered AN patients than in HC in the L superior temporal sulcus and L subcentral gyrus and sulcus and lower FD in in the bilateral superior parietal lobule, L postcentral gyrus, R intraparietal sulcus and bilateral parieto-occipital sulcus. Negative correlations between whole-brain FD and age (all groups), duration of illness (AN) and age of onset (rec-AN). Positive correlations between whole-brain FD and cortical volume (all groups), BMI (AN) and gyrification index (HC).
Cook et al. (1995)	UK Australia	Case–control	Frontal lobe epilepsy (16) Temporal lobe epilepsy (10) HC (20)	44%	28.3 (8.2)	1.5 T	2D box-counting	1.34 (.06) [1.32, 1.48] 1.45 (.06)	9 out of 16 patients with FLE had abnormal FD values. All patients with TLE had normal FD values.

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Esteban et al. (2009)	Spain	Case–control	Multiple sclerosis (52) HC (20)	69% 60%	35.3 (8.8) 37.4 (8.7)	1.5 T	3D box-counting (SPM2, custom script)	2.68 (.001) 2.67 (.001)	Higher FD in multiple sclerosis (MS) patients than in HC ($p < .001$). Higher FD in the late stage of the disorder (RRMS) than at the first episode (FAMS) ($p < .05$). Positive correlation between FD and lesion load of MS in T1 and T2 images ($p = .05$, $p = .017$).
Free et al. (1996)	UK Australia	Case–control	Cryptogenic epilepsy (39) HC (30)	49% 33%	27	1.5 T	Dilation algorithm	2.30 (.09)	HC: No differences between male and female participants. Higher FD at the poles than in the central portion of the brain; symmetric FD between hemispheres ($p < .05$). Cryptogenic epilepsy patients: 16 out of 39 patients had abnormal FD values in at least one portion of the brain.
Goñi et al. (2013)	USA Spain	HC	HC USA (50) HC Spanish (24)	0% 67%	24 (3.2) 57 (8.6)	3.0 T	3D box-counting (FreeSurfer 5.1.0, custom script)		Averaging FD values across multiple box-size ranges and grid offsets ensures a high consistency (intraclass correlation). Using a single grid scale and offset results in low test–retest reliability.

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TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Hedderich et al. (2020)	Germany	Case–control	Very preterm/very low birth weight (101) HC (111)	43% 41%	26.7 (.6) 26.8 (.7)	3.0 T	Spherical harmonic reconstructions (SPM12, CAT12)		Lower FD in very preterm/very low birth weight individuals than in HC in bilateral medial parietal cortex; bilateral lateral temporal cortex; R frontal operculum; R occipitotemporal junction Positive correlation between gestational age and FD of bilateral medial parietal cortex (L: $p < .001$; R: $p = .014$). Positive correlation between birth weight and FD of R medial parietal cortex ($p < .01$) and R lateral temporal cortex ($p = .002$). Positive correlation between WAIS scores and FD of bilateral medial parietal cortex (L: $p < .020$; R: $p = .002$) and L lateral temporal cortex ($p = .039$).
Hou et al. (2020)	China	Case–control	Ultrahigh risk for psychosis (36) HC (59)	67% 46%	19.1 (.7) 20.5 (1.1)	3.0 T	Spherical harmonic reconstructions (SPM12, CAT12)		No significant differences in FD values between groups.
Huang et al. (2017)	Taiwan	Case–control	Spinocerebellar ataxia type 3 (40) HC (40)	50% 50%	45.9 (11.9) 43.5 (11.2)	1.5 T	3D box-counting (SPM8)		Lower FD in spinocerebellar ataxia patients than HC in the bilateral anterior lobe ($p < .001$), posterior upper lobe ($p < .001$), posterior lower lobe ($p < .05$) and cerebellum ($p < .001$).

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Im et al. (2006)	South Korea	HC	HC (44)	45%	26.4 (5.5)	1.5 T	3D box-counting (mixed softwares, FD3)		FD values were significantly predicted by: Cortical thickness (CT) and folding area (FA) in both hemispheres (L: $p < .001$; R: $p < .001$) FA in bilateral parietal lobes (L: $p = .004$; R: $p < .001$); in L frontal lobe ($p = .017$); and FA in L temporal lobe ($p = .001$). Positive correlation between FD and years of education (L: $p = .002$; R: $p < .021$) and IQ (R: $p = .043$).
Jao et al. (2021)	Taiwan	Cross-sectional	Young (66) Middle (98) Old (94)	45% 42% 44%	39.5 (6.1) 53.7 (4.3) 67.4 (4.9)	3.0 T	2D box-counting (SPM8, HarFA)	2.296	Lower FD in middle (M) participants than in young (Y) in bilateral frontal, L temporal and R limbic lobes. Lower FD in old (O) than in M in temporal, parietal and L limbic lobes. Higher FD in O than in M in the occipital lobe. In the Y group, female participants exhibited more hemispheric asymmetries, while male participants showed them only in the M and O groups. Male participants displayed earlier and more significant FD reduction across age. (Significance threshold: $p < .05$)

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Jiang et al. (2008)	China	HC	HC (57)	53%	23.6 (3.9)	3.0 T	3D box-counting (FreeSurfer, custom script)		Positive correlation between FD and FA in both hemispheres (L: $p < .001$; R: $p < .001$) and in the bilateral prefrontal (L: $p < .001$; R: $p < .001$), parietal (L: $p < .001$; R: $p < .001$), temporal (L: $p = .008$; R: $p = .011$) and occipital (L: $p < .001$; R: $p = .001$) lobes. Positive correlation between FD and absolute curvature in the L hemisphere ($p = .015$) and in the R occipital ($p = .046$) and bilateral prefrontal lobes (L: $p < .001$; R: $p = .035$). Negative correlation between FD and CT in the R hemisphere ($p = .012$) and parietal lobe ($p = .016$).
Kalmanti and Maris (2007)	Greece	Cross-sectional	HC (93)	40%	16.6 (16.6)	1.5 T	2D box-counting (ImageJ)		Higher FD in the lateral left hemisphere ($p < .03$). Negative correlation between age and FD of both hemispheres in the 1–15 age range. Negative correlation between age and FD of the L lateral cortex in infants. Negative correlation between age and FD of the R lateral and middle cortex in participants older than 15 years.

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
King et al. (2010)	USA	Case–control	Alzheimer's disease (35) HC (35)	Whole = 44%	75.4 (7.1) 75.0 (5.0)		3D box-counting (FreeSurfer, C3)		Lower FD in patients with Alzheimer's disease than in HC for the grey/white matter surface ($p < .05$) and cortical ribbon ($p < .001$). Positive correlation between FD and gyrification index of the pial surface ($p < .001$), grey/white matter surface ($p < .001$) and cortical ribbon. Positive correlation between FD of the cortical ribbon and cognitive functioning ($p = .002$).
King et al. (2009)	USA	Case–control	Mild–moderate Alzheimer's disease (15) HC (15)	53% 53%	75.7 (9.6) 76.1 (7.8)	1.5 T 3.0 T	2D box-counting (FreeSurfer, FDC)		Lower FD in patients with Alzheimer's disease than in HC in all coronal slices, and in 2 (out of 3) axial slices.

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Kinno et al. (2017)	Japan	Cross-sectional	Alzheimer's disease (23) Mild cognitive impairment (14) Vascular dementia (2) Diffuse Lewy body disease (2) Frontotemporal Dementia (3) Idiopathic normal pressure Hydrocephalus (1) HC (5)	Whole = 58%	Whole: <75	1.5 T	Spherical harmonics reconstructions (SPM12, CAT12)		Positive correlation between performance on the Wechsler Memory Scale-Revised and FD of L and R frontotemporal regions. The factor 'recognition memory' was most robustly correlated with the FD of the L frontotemporal regions. The factors 'visual and working memory' and 'attention' were most robustly correlated with the FD of the R frontotemporal regions. The factor 'attention' was selectively correlated with the FD of the R precuneus, R pericalcarine cortex and cuneus. The factor 'visual and working memory' was selectively correlated with the FD of the L lateral occipital cortex.
Krohn et al. (2019)	Germany	HC	HC (11)	54%	[24, 34]	3.0 T	3D box-counting (FSL, calcFD)		Optimization of the spatial scale greatly improves accuracy of FD calculation. Registration to the first T1 volume has a significant effect on FD but with different directions depending on the image sequence, resolution and whether skeletonization has been applied. Reregistration to MNI template mitigated these effects.

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Kubera, Schmitgen, Hirjak, et al. (2019)	Germany	Case–control	Pre-Huntington's disease (57) HC (57)	58% 47%	38.8 (9.1) 38.8 (9.8)	3.0 T	Spherical harmonics reconstruction (SPM12, CAT12)		Lower FD in pre-Huntington disease (HD) patients than in HC in a cluster including supramarginal and postcentral cortex, precentral cortex and lingual gyrus in the L hemisphere and in precuneus, posterior and middle cingulate gyrus and lingual gyrus in the R hemisphere. Higher FD in pre-HD than in HC in middle and superior temporal cortex in the L hemisphere. In pre-HD, FD was lower than in HC. (Significance threshold: $p < .05$)
Kubera, Schmitgen, Nagel, et al. (2019)	Germany	Case–control	Parkinson's disease (22) HC (18)	64% 50%	64.6 (2.2) 62.7 (2.3)	3.0 T	Spherical harmonic reconstructions (SPM12, CAT12)		No significant differences in FD values between groups.
D. Li, Wang, et al. (2020)	China	Case–control	Parkinson's disease (60) HC (56)	50% 45%	61.6 (6.9) 63.1 (5.5)	3.0 T	Spherical harmonic reconstructions (SPM12, CAT12)		Lower FD in Parkinson's disease patients than in HC in the L precentral and postcentral cortex, L superior frontal cortex, L caudal middle frontal cortex, bilateral superior parietal cortex and R superior temporal cortex. (Significance threshold: $p < .05$)

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Li et al. (2011)	China	Cross-sectional	HC (259)	63%	[18, 94]	1.5 T	3D box-counting (MRIcro, custom script)		Negative relation between age and FD of posterior wall of the right central sulcus ($p = .005$).
Z. Li, Zhang, Wang, et al. (2020)	China	Case–control	Benign childhood epilepsy with centrotemporal spikes (25) HC (20)	52% 30%	9.1 (1.6) 9.5 (1.5)	3.0 T	Spherical harmonic reconstructions (SPM12, CAT12)		No significant differences in FD values between groups.
Li, Zhang, Li, et al. (2020)	China	Case–control	Non-syndromic lip and palate cleft (NSCLP) after palatoplasty without articular rehabilitation (24) NSCLP after palatoplasty and AR (21) HC (24)	50% 33% 37%	23.0 24.0 22.0	3.0 T	Spherical harmonic reconstructions (SPM12, CAT12)		Lower FD in the NSCLP patients after rehabilitation training than in HC in tight inferior parietal lobule. Positive correlation between whole-brain FD and IQ and other cognitive scores in NSCLP group. (Significance threshold: $p < .05$)
Lin et al. (2007)	USA	Case–control	Right mesial temporal lobe epilepsy (15) Left mesial temporal lobe epilepsy (15) HC (19)	73% 33%	31.9 (9.7) 30.8 (8.4)	1.5 T	Spherical parametrization (n.a., custom script)		Lower FD in L and R mesial temporal lobe epilepsy (MTLE) patients than in HC in bilateral temporal, L parietal and bilateral occipital regions. Lower FD in LMTLE patients than in HC in L frontal and R parietal regions. No correlations between cortical thickness and FD.
Liu et al. (2020)	Australia	Longitudinal	HC (161)	54%	Baseline: 77.1 (4.1) 2-year follow-up: 79.0 (4.1) 6-year follow-up: 83.0 (4.1)	3.0 T	Dilation algorithm (FreeSurfer 5.3.0, calcFD)	[2.21, 2.33] [2.18, 2.30]	Longitudinal decrease in the FD of all cortical areas and subcortical structures, except for the bilateral pallidum and accumbens. Higher FD in males than in females in the L thalamus, R pallidum and bilateral amygdala.

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Lu (2020)	China	Cross-sectional	Young (25–35 years) (35) Middle-aged (36–60 years) (62) Young-old (61–75 years) (62) Old-old (over 75 years) (55)	41% 32% 32% 31%	30.1 (3.8) 50.2 (5.4) 72.1 (3.9) 86.2 (3.9)	1.5 T	3D box-counting (SPM12, custom script)		Lower FD in old than young adults in the left DLPFC ($p < .001$). No difference between young-old and old-old adults. Negative correlation between age and FD of left DLPFC ($p < .001$).
Madan (2018)	UK	HC	HC (648)	50%	54.2 (18.5)	3.0 T	3D box-counting (FreeSurfer 6.0, calcFD)		Negative correlation between FD and age ($p < .001$). The impact of head motion on morphology measures (including FD) is limited but increased during the presentation of a movie.
Madan (2021)	UK	Longitudinal	HC (280)		[45–92]	3.0 T	3D box-counting (FreeSurfer, calcFD)		FD decreases with aging ($p < .001$).
Madan and Kensinger (2017)	China USA	HC	HC China (30) HC USA (1570)		[20, 30] [18, 25]	3.0 T	Dilation, 3D box-counting, spherical harmonics reconstructions (FreeSurfer 5.3.0, calcFD/SPHARM)		FD was found to have a high test–retest reliability (intraclass correlation) both globally and for individual regions. The spherical harmonics algorithm yielded the highest intraclass correlation. The reliability of regional FD was higher than that of cortical thickness.

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Madan and Kensinger (2016)	USA	Cross-sectional	GH dataset (251) HH dataset (129) IP dataset (47)	29% 63% 68%	[20, 86] [20, 81] [21, 78]	1.5 T 3.0 T 1.5 T	3D box-counting (FreeSurfer 5.3.0, calcFD)		Negative correlation between FD (filled volume: $p < .001$; surface: $p < .001$) and age. High correlations between the FD from filled volumes and FD from the surface ($p < .001$). FD is more strongly related to age than cortical thickness and gyrification.
Madan and Kensinger (2018)	USA UK	Cross-sectional	IXI dataset (427) OASIS dataset (314) DLBS dataset (315)	61% 62% 63%	[20, 86] [18, 94] [20, 89]	3.0 T 1.5 T 3.0 T	3D box-counting (FreeSurfer 5.3.0, calcFD)		FD was most affected by age in the superior temporal gyrus and inferior parietal lobule. FD is more strongly related to age than cortical thickness and gyrification.
Marzi et al. (2018)	Italy	Longitudinal	Spinocerebellar ataxia type 2 (9) HC (16)	33% 44%	48.7 (12.9) 50.3 (18.8)	1.5 T	3D box-counting (FreeSurfer 5.3.0, calcFD)	2.39 (.03) 2.43 (.02)	Lower FD of cerebellar grey ($p < .001$) and white ($p < .001$) matter in spinocerebellar ataxia (SCA) patients than in HC. Lower FD of cortical grey matter in SCA patients than in HC ($p = .002$). No significant differences in rate of change of FD values between controls and SCA patients were found between T0 and T1.
Marzi et al. (2020)	Italy	Cross-sectional	NKI2 dataset (73) ICBM dataset (86)	41% 52%	11.8 (3.1) 44.2 (17.1)	3.0 T 3.0 T	2 a priori and 2 automated methods for spatial scales 3D box-counting (FreeSurfer 5.3.0, calcFD)	[2.26, 2.55] [2.26, 2.50]	Negative correlations between FD and age emerged only with automated strategies.

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
McDonough and Madan (2021)	USA	Case–control	People at risk of dementia (63) HC (18)	65% 56%	60.2 (6.8) 23.2 (3.0)	3.0 T	Haussdorf dimension (FreeSurfer 6.0, calcFD)		Subcortical FD was more strongly negatively correlated with age than cortical FD. Cortical FD was negatively associated with brain activity during memory retrieval in medial and lateral parietal cortices uniquely in middle-aged and older adults. The lower FD–higher brain activity pattern was associated with poorer cognition.
Mustafa et al. (2012)	UK	Cross-sectional	HC (217)	47%	68	1.5 T	3D box-counting (FreeSurfer)	Males: 2.50 (.03) Females: 2.50 (.02) Whole sample: 2.50 (.03)	Positive correlation between FD and total intracranial volume (TICV), brain volume and WM volume (WMV) in women. Positive correlation between FD and brain volume and WMV in men. Positive correlation between FD and the performance on Raven's progressive matrices. Positive correlation between FD and lifelong fluid intelligence change. Negative correlation between FD and decline in cognition in late life.
Narr et al. (2001)	UK	Case–control	Chronic schizophrenia (25) HC (28)	40% 46%	31.1 (5.6) 30.5 (8.7)	1.5 T	Dilation algorithm (n.a., custom script)		Significant diagnosis-by-hemisphere interaction for gyral complexity in the superior frontal cortices ($p < .01$). Higher FD in male than in females in inferior frontal regions ($p < .01$).

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Nenadic et al. (2017)	Germany	Case–control	Bipolar disorder (18) HC (26)	61% 42%	40.1 (10.2) 35.6 (10.4)	3.0 T	Spherical harmonic reconstructions (FreeSurfer)		Higher FD in bipolar patients than in HC in L orbitofrontal cortex and R precuneus ($p < .05$ uncorrected). Lower FD in bipolar patients than in HC in R caudal middle frontal, R entorhinal cortex, R pars orbitalis, L fusiform cortex and L posterior cingulate cortex ($p < .05$ uncorrected).
Nenadic and Yotter (2014)	Germany	Case–control	Schizophrenia (87) HC (108)	45% 37%	35.5 (11.0) 32.2 (10.0)	1.5 T	Spherical harmonic reconstructions (FreeSurfer 4.5)		Lower FD in the negative schizophrenia subgroup than in HC in the R hemisphere ($p < .001$), L anterior cingulate ($p < .05$), L superior frontal ($p < .05$), L precentral and R superior parietal ($p < .05$). No significant differences in FD between the disorganized schizophrenia subgroup and HC. Lower FD in the paranoid schizophrenia subgroup than in HC in the R hemisphere ($p < .001$) and in the R superior parietal lobe ($p < .05$).

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Nicastro et al. (2020)	Italy	Case–control	Alzheimer's disease (32) Frontotemporal dementia (24) HC (28)	44% 50% 46%	72.3 (8.2) 66.2 (9.2) 70.3 (5.6)	3.0 T	Spherical harmonic reconstructions (SPM12, CAT12)	2.54 (.02) 2.54 (.03) 2.56 (.02)	Lower FD in Alzheimer's disease patients than in HC in the whole brain ($p < .001$), insula ($p < .05$), posterior cingulate ($p < .05$), precentral and postcentral gyri ($p < .05$; $p < .05$) and parahippocampal regions ($p < .05$). Lower FD in frontotemporal dementia patients than in HC in the whole brain ($p < .001$), insula ($p < .05$), posterior cingulate ($p < .05$) and precentral and postcentral gyri ($p < .05$). Positive correlation between FD and cortical thickness ($p = .005$). Frontotemporal dementia subtypes showed a variable degree of FD reduction in the insula, orbitofrontal and middle frontal regions.
Nickel et al. (2019)	Germany	Case–control	Anorexia nervosa (34) Recovered from AN (24) HC (41)	100% 100% 100%	23.8 (4.3) 27.1 (7.0) 23.6 (3.8)	3.0 T	Spherical harmonic reconstructions (SPM12, CAT12)		No significant difference in FD between anorexia nervosa patients and HC. Trend for lower FD in anorexia nervosa patients than in HC in the L middle occipital gyrus. Trend for higher FD in anorexia nervosa patients than in HC in the L precentral gyrus.

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Pantoni et al. (2019)	Italy	Case–control	Small vessel disease with MCI (76) HC (24)	47% 50%	74.6 (6.9) 72.5 (4.7)	1.5 T	3D box-counting (FreeSurfer 5.3, custom script)	2.44 (.02) 2.43 (.02)	Lower white matter ($p = .006$) and grey matter ($p = .015$) FD in the small vessel disease patients than in HC. White matter FD decrease consistently predicts worse cognitive performance.
Rajagopalan and Pioro (2021)	USA	Case–control	Amyotrophic lateral sclerosis (ALS) typical (19) ALS with upper motor neuron (UMN) dysfunction and corticospinal tract (CST) hyperintensity (17) ALS with UMN without CST hyperintensity (25) ALS patients with frontotemporal dementia (14) HC (14)	42% 29% 40% 79% 36%	57.5 (12.2) 51.7 (11.6) 59.4 (10.5) 67.4 (10.2) 51.7 (15.7)	1.5 T	3D box-counting (Matlab)		Lower FD in patients with ALS and frontotemporal dementia than in HC or between ALS groups in R primary motor cortex, bilateral sensory cortex and whole brain.
Ruiz de Miras et al. (2017)	Spain	Case–control	Alzheimer's disease (33) Mild cognitive impairment (122) HC (32)	70% 53% 50%	75.7 (3.7) 73.2 (5.7) 72.7 (5.9)	3.0 T	Spherical harmonic reconstruction (FreeSurfer)		Lower FD in Alzheimer's disease patients and in converters patients with MCI than in HC. Lower FD in converters MCI patients than in nonconverters MCI patients. Positive correlation between FD and cognitive functioning. (Significance threshold: $p < .05$)
Sandu, Specht, et al. (2008)	Norway	Case–control	Dyslexia (13) HC (18)	39% 56%	13.2 (.4) 13.5 (.5)	1.5 T	3D box-counting (Brain-Voyager)		Higher FD in girls with dyslexia than HC girls in L hemisphere ($p < .05$).
Sandu, Rasmussen, et al. (2008)	Norway	Case–control	Schizophrenia (7) HC (6)			1.5 T	3D box-counting, Minkowski–Bouligand (Brain-Voyager)	2.48 (.01) 2.47 (.01)	Higher FD in patients with schizophrenia than in HC ($p < .05$).

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Sandu et al. (2014)	Norway	Case–control	Adolescents (17) Young adults (14)	65% 50%	14.1 (.3) 24.2 (2.8)	1.5 T	3D box-counting, Minkowski–Bouligand (FreeSurfer)		Lower FD in young adults than in adolescents in whole brain, left and right hemisphere, frontal and parietal lobes (both genders), L temporal lobe (males). (Significance threshold: $p < .05$)
Schmitgen et al. (2019)	Germany	Case–control	Treatment-resistant depression (12) HC (12)	67% 67%	46.3 (11.3) 43.5 (11.5)	3.0 T	Spherical harmonic reconstructions (SPM12, CAT12)		Lower FD in patients with treatment-resistant depression than in HC in the R caudal middle frontal gyrus ($p < .05$ uncorrected).
Schmitt et al. (2021)	Germany	Cross-sectional	HC Marburg (377) HC Munster (203)	61% 63%	34.6 (12.6) 28.14 (10.1)	3.0 T	Spherical harmonic reconstructions (SPM12, CAT12)		Negative association between polygenic risk for major depression and FD in the R orbitofrontal cortex ($p < .001$).

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Sheelakumari et al. (2017)	India	Case–control	Behavioural frontotemporal dementia (27) Primary progressive aphasia (12) HC (20)	37% 41% 35%	61.2 (11.9) 64.6 (4.0) 61.1 (6.2)	1.5 T	3D box-counting (SPM8, custom script)	2.54 2.54 2.57	Lower FD in patients with frontotemporal dementia (FTD) than in HC in whole brain and R hemisphere (skeleton, general structure). Lower FD in patients with primary progressive aphasia (PPA) than in HC in whole brain and L hemisphere (skeleton, general structure). Lower whole-brain FD in FTD patients than in PPA patients (skeleton, general structure) No significant differences in surface FD between groups. Negative correlation between right hemisphere skeleton FD and scores at the frontal system behaviour scale in FTD patients (Significance threshold: $p < .05$)
Squarcina et al. (2015)	Italy	Case–control	Schizophrenia (25) Bipolar disorder (11) HC (39)	40% 55% 56%	35.0 (7.7) 41.0 (8.9) 28.4 (5.4)	3.0 T	3D box-counting (FSL)		Lower FD in patients with schizophrenia and bipolar disorder than HC.
Tae et al. (2005)	South Korea	Case–control	Schizophrenia (45) Obsessive–compulsive disorder (OCD) (50) HC (26)	42% 32% 38%	27.0 (5.4) 26.7 (7.0) 24.1 (4.8)	1.5 T	3D box-counting (Analyze, custom script)	2.37 (.031) 2.39 (.021) 2.42 (.017)	Lower whole-brain FD in schizophrenia patients than in OCD patients ($p < .017$). Lower whole-brain FD in OCD patients than in HC ($p < .001$). Significant group-by-hemisphere interaction ($p = .009$).

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Thompson et al. (2005)	USA	Case–control	Williams syndrome (42) HC (40)	55% 60%	29.2 (9.0) 27.5 (7.4)	1.5 T		2.25 (.0) 2.24 (.0)	Higher FD in patients with Williams syndrome than HC. In both hemispheres (L: $p = .001$; R: $p = .001$).
Wang et al. (2015)	Taiwan	Case–control	Spinocerebellar ataxia type 3 (48) HC (50)	44% 50%	48.1 (11.7) 48.2 (14.0)	1.5 T	3D box-counting		Lower FD in spinocerebellar ataxia patients than in HC in widespread areas across the cerebellar and cerebral cortex. Negative correlation between disease duration and FD of the cerebral and cerebellar cortex. Negative correlation between symptom severity and FD of the cerebellar cortex ($p = .023$).
Wolf et al. (2021)	Germany	Case–control	Schizophrenia with parkinsonism (38) Schizophrenia without parkinsonism (35) HC (20)	45% 54%	41.7 (11.8) 40.4 (10.6)	3.0 T	Spherical harmonic reconstructions (SPM 12, CAT 12)		Higher FD in schizophrenia patients with parkinsonism than in patients without parkinsonism in the left supplementary motor cortex ($p < .05$). No differences in FD between patients and HC.
Wu et al. (2009)	Taiwan	Case–control Cross-sectional	Mixed pathologies (12)HC (32)		Whole: [22, 36] weeks of gestation	1.5 T	3D box-counting (n.a. HarFa)		Positive correlation between age and FD of the foetal cortical surface. Lower FD in twins and foetuses with cortical dysplasia than in HC. (Confidence interval: 95%)
Yotter et al. (2011)	Germany	Case–control	Schizophrenia (87) HC (108)	45% 37%	35.5 (11.0) 32.1 (10.0)	1.5 T	Spherical harmonic reconstructions (FreeSurfer 4.5, custom script)		Lower FD in schizophrenia patients than in HC in R hemisphere ($p < .001$), bilateral precentral gyrus, L caudal anterior cingulate, L frontal pole, Rlingual gyrus and R superior parietal lobe.

(Continues)

TABLE 1 (Continued)

Authors (year)	Country	Design	Sample groups (*N*)	*F* %	Age *M* (*SD*) [range]	MR strength	FD algorithm (software)	FD *M* (*SD*) [FD range]	Main findings
Zhao et al. (2018)	China	Case–control	Autism spectrum disorder (ASD) (20) HC (18)	0% 0%	8.8 (1.1) 8.9 (1.2)	3.0 T	3D box-counting (FreeSurfer, custom script)		Lower FD of the R cerebellar cortex in patients with ASD than in HC children ($p = .006$). ASD children with higher performance IQ relative to verbal IQ showed higher FD values, closer to HC children ($p = .023$).
Zhuo et al. (2020)	China	Case–control	Auditory verbal hallucinations (42) HC (50)	33% 28%	23.9 (1.5) 24.9 (2.2)	3.0 T	Spherical harmonic reconstructions (SPM12, CAT12)		Higher FD in patients with auditory verbal hallucinations than in HC in the L Wernicke area, L Broca area and L parietal lobe. No correlation between FD and symptoms. (Significance threshold: $p < .05$)

psychiatric disorders, FD in neurological disorders and FD in other disorders.

3 | RESULTS

3.1 | Estimation reliability

Six studies assessed the reliability of FD and possible factors that could influence the various algorithms used to compute it.

Goñi et al. (2013) conducted a thorough investigation of the reliability of the 3D box-counting method in the different algorithms, parameters and brain objects that can be used when computing FD. The authors observed that the algorithm with the highest FD values and intraclass correlation (ICC) is the correlation dimension, followed by the information dimension and Kolmogorov capacity dimension in this order. The article also states that the ICC increases with the number of grid offsets used reaching a plateau around 15 mm and that the number of box sizes has a similar effect yet less pronounced. Furthermore, rather than relying on the minimal or maximal box counts resulting from the various combinations of the other two parameters described above, the reproducibility of FD improves dramatically when using its average. Finally, FD estimations were more reliable when inferred from the GM–WM interface or the WM volume.

A second study (Krohn et al., 2019) instead investigated the effects of different MRI characteristics and processing protocols on FD. Deviation analyses showed a good robustness of the fractality estimates that was improved by image registration to common templates, which also regularized their distribution. Image reregistration, in fact, was associated with a complex set of effects on FD measures whose magnitude and direction varied as functions of image weighting, resolution and skeletonization. Furthermore, the authors observed that both T1- and T2-based FD values were significantly affected by resolution, registration, binarization and skeletonization, in a very similar manner. For example, low-resolution images led to consistently lower fractality values. The authors attribute this result to the partial volume effect typical of coarse resolution that causes a blunting of structural features of the cortex (Madan, 2018).

Krohn et al. (2019) also proposed a procedure to optimize the grid-scale range by minimizing the R^2 of the FD regression, which significantly improves the accuracy of the estimation. This and three other strategies to select grid scales (Goñi et al., 2013; Kiselev et al., 2003; Marzi et al., 2020) were compared by Marzi et al. (2020) using age-prediction accuracy as an index of reliability. They observed that automated optimization methods that rely on R^2 minimization led to a smaller prediction error compared with strategies that impose a priori limits, especially if they also maximize the number of scales.

Furthermore, Madan and Kensinger (2017) conducted a systematic comparison of the test–retest reliability of the three FD-estimation algorithms. The spherical harmonic reconstructions yielded the highest ICC of surface-based estimations, while the dilation algorithm ensured the best replicability of volume FD. Furthermore, compared with other morphological measures (i.e., cortical thickness and gyrification), FD was found to be more consistent and less sensitive to head motion than other cortical measures (Madan, 2018).

From these findings emerges that FD estimates are sensitive to multiple aspects of data acquisition and processing, causing research findings to be relatively fragmented and preventing real direct comparisons (e.g., a meta-analysis) among them.

3.2 | Comparison with other cortical measures

The relationship between FD and other cortical measures has been assessed in several studies (Im et al., 2006; Jiang et al., 2008; Lu, 2020; Madan & Kensinger, 2016; Sandu et al., 2014).

Im et al. (2006) observed that FD was positively associated with the folding area (FA) and negatively associated with the cortical thickness in both hemispheres. These results were replicated by Jiang et al. (2008), who also observed a positive correlation between FD and the standard deviation of the absolute mean curvature of the vertices in the left hemisphere. Regarding cortical thickness, a contrasting result has been reported instead by Madan and Kensinger (2016), who observed a positive relationship between whole-brain FD and cortical thickness.

Only two studies analysed the relationship between FD and the GI and obtained opposite results. In fact, while Madan and Kensinger (2016) reported that the two measures were positively correlated, Lu (2020) observed a negative correlation between the GI and the FD of the left dorsolateral prefrontal cortex (DLPFC).

According to the results provided by Lu, left DLPFC FD was also negatively associated with cerebrospinal fluid (CSF) volume and positively correlated with GM volume and density. Lastly, Sandu et al. (2014) also reported the positive association between GM volume and FD.

3.3 | Healthy subjects

3.3.1 | Development and aging

Fourteen of the retrieved studies analysed the relationship between FD and age in healthy individuals.

Of these, one (Wu et al., 2009) examined MR images of foetuses at the 22nd to 36th week of gestation (healthy and with mixed pathologies) calculating FD using the 3D box-counting method. The results revealed that during this early period of development FD values tend to increase with gestational age. In fact, in the presence of delays in the maturational trajectory (i.e., cortical dysplasia and twins), cortical FD was reduced (which did not occur for any other clinical condition). However, this trend appears to change during postnatal development.

Four of the studies focused their attention on the development of FD from childhood to adulthood (Blanton et al., 2001; Kalmanti & Maris, 2007; Marzi et al., 2020; Sandu et al., 2014). In particular, Kalmanti and Maris (2007) estimated the 2D FD of sagittal images in infants (<1 year), children (1–10 years), adolescents (10–15 years) and adults (>15 years). The authors observed that age was negatively correlated with FD of the left hemisphere in infants, of both hemispheres in children and adolescents, and of the right hemisphere in adults. Two studies analysed the relationship between age and 3D FD in children aged 6 to 16 years; however, they obtained contrasting results. In fact, while Blanton et al. (2001) observed an increase in FD with age, especially in the frontal lobes, Marzi et al. (2020) reported a significant negative correlation between FD of the whole brain and age, similar to what Kalmanti and Maris observed with 2D FD. Sandu et al. (2014), which evaluated differences in FD between adolescents (13–14) and young adults (20–30 years), also reported a similar result, and observed a significant reduction in FD from adolescence to adulthood. Given these conflicting findings, it is apparent that differences in FD estimation can yield opposing findings.

Nine studies analysed FD in healthy adult and elderly participants, and all observed a general reduction in FD with age (Jao et al., 2021; Li et al., 2011; Liu et al., 2020; Lu, 2020; Madan & Kensinger, 2018, 2016; Marzi et al., 2020; McDonough & Madan, 2021; Madan, 2021). A negative relationship between age and FD has been reported both at the whole-brain level (Madan & Kensinger, 2016, 2018; Marzi et al., 2020; McDonough & Madan, 2021) and at the regional level in the left DLPFC (Lu, 2020) and in the posterior wall of the right central sulcus (Li et al., 2011). Jao et al. (2021) reported regional differences in FD between young adults (<45 years), middle adults (46–60 years) and old adults (>60 years) and observed a reduction in FD from young to middle age in the bilateral frontal, left temporal and right limbic lobes and a reduction in FD from middle to old age in the bilateral temporal, parietal and left limbic lobes. However, they also observed an increase in FD of the left middle orbitofrontal cortex from young to middle age and of the occipital lobe from middle to old age.

The two longitudinal studies conducted so far obtained results in line with the above cross-sectional studies (Liu et al., 2020; Madan, 2021). More specifically, Liu et al. estimated FD in old adults at baseline (70–90 years) and after 2 and 6 years and observed a significant reduction in FD in all the cortical and subcortical regions analysed, except for the pallidum and nucleus accumbens, which did not change during the 6 years. Madan, instead, estimated whole-brain FD changes from baseline to up to 10 years in a group of 280 healthy individuals, and observed a negative relationship between FD and age.

Regarding other cortical measures, such as cortical thickness or GI, FD seems to be more sensitive to age-related differences, and, in the study conducted by Madan and Kensinger (2018), interindividual differences in FD could explain more than 70% of the variance in age.

Lastly, two studies observed that the decrease in FD was faster and more significant in males than in females (Jao et al., 2021; Li et al., 2011).

3.3.2 | Cognition

Six of the 52 retrieved studies analysed the relationship between FD and cognitive functioning (Im et al., 2006; Kinno et al., 2017; Liu et al., 2020; Lu, 2020; McDonough & Madan, 2021; Mustafa et al., 2012). Except for Lu (2020), who did not observe any association between FD and scores obtained at the Mini-Mental State Examination, all other studies reported that higher FD values were generally associated with higher cognitive performance. In particular, Im et al. (2006) observed a positive relationship between FD of the whole brain and years of education and between FD of the right hemisphere and IQ in a sample of healthy young adults.

Liu et al. (2020) analysed the relationship between FD and cognition in older individuals (70–90 years) and observed significant correlations between FD and global cognition in the bilateral temporal lobe, left occipital lobe and several subcortical structures. Mustafa et al. (2012), who estimated WM FD in subjects of 68 years of age, reported similar results and observed a positive correlation between whole-brain FD and the scores obtained in the Raven's progressive matrices test. Furthermore, they also observed a positive correlation between FD and estimated lifelong changes in fluid abilities and a negative correlation between FD and estimated cognitive decline.

McDonough and Madan (2021) analysed the relationship between FD, brain activity and cognitive functioning in middle-aged and old individuals at risk of dementia. Their results show that reduced FD was associated with increased brain activity during memory retrieval in several posterior brain regions and that this pattern was associated with poorer cognitive functioning.

Lastly, Kinno et al. (2017) analysed the relationship between FD and memory functioning in a sample of old individuals (>75 years) with different neurological diseases, and they observed significant positive correlations between the scores obtained in the Wechsler Memory Scale-Revised (WMS-R) and the FD of several frontotemporal regions.

3.4 | Psychiatric disorders

3.4.1 | Schizophrenia spectrum disorders

Ten of the retrieved studies evaluated FD in schizophrenia spectrum disorders. Of 10, eight involved patients with schizophrenia, one involved individuals at ultrahigh risk of psychosis (Hou et al., 2020) and one involved individuals with auditory verbal hallucinations (Zhuo et al., 2020).

Among the studies that evaluated differences in FD between patients with schizophrenia and HCs, only one study reported significantly higher FD values in patients than in controls, for both the total volume of the brain and the right hemisphere (Sandu, Specht, et al., 2008). Two studies did not report significant differences in overall FD between patients and HC (Bullmore et al., 1994; Narr et al., 2001), and three studies reported a reduction in FD in schizophrenia patients, for the whole brain (Squarcina et al., 2015; Tae et al., 2005) or for the right hemisphere only (Yotter et al., 2011). Yotter et al. (2011) also assessed regional differences in FD and observed a reduction in FD in patients with schizophrenia in the right superior parietal lobe.

Nenadic and Yotter (2014) divided a sample of schizophrenia patients, the same as in Yotter et al. (2011), into three subgroups with predominantly negative, disorganized and paranoid symptoms. Their results showed that the negative subgroup had a reduction in FD, compared with HC, globally in the right hemisphere and regionally in the left caudal anterior cingulate, left precentral, left superior frontal and right superior parietal regions. The paranoid subgroup showed reduced FD in the right hemisphere and in the right superior parietal lobe, while the disorganized group did not differ from HC in FD measures.

In a recent study, Wolf et al. (2021) explored cortical complexity in two groups of schizophrenia patients, with and without parkinsonism. Compared with patients without parkinsonism, patients with parkinsonism showed increased cortical complexity in the left supplementary motor cortex. No differences were detected in the same area between the experimental samples and HCs.

Two studies (Narr et al., 2001; Tae et al., 2005) also evaluated differences between patients and HC in FD hemispheric asymmetry. Both studies observed a significant diagnosis-by-hemisphere interaction; however, their results are quite inconsistent. While Tae et al. observed a rightward asymmetry for both patients and HC, with patients showing a more prominent reduction in left hemisphere FD, Narr et al., who also observed a rightward asymmetry in the HC group, reported a leftward asymmetry in patients with schizophrenia.

The only study conducted in individuals at high risk for psychosis did not show significant differences in FD between high-risk and low-risk individuals (Hou et al., 2020).

Lastly, the study conducted by Zhuo et al. (2020) revealed that individuals with auditory verbal hallucinations had increased FD in the left Wernicke area, the left Broca area and the left parietal lobe.

3.4.2 | Bipolar disorder

Three studies analysed FD in patients with bipolar disorder (Bullmore et al., 1994; Nenadic et al., 2017; Squarcina et al., 2015). Bullmore et al. (1994) used a box-counting estimate of FD for the boundary between white and GM and observed an increase in FD in patients with bipolar disorder compared with HC. In contrast to what Bullmore et al. observed, Squarcina et al. (2015), who also adopted a box-counting algorithm, observed an overall reduction in FD in patients affected by bipolar disorder, especially in the frontal lobe. Nenadic et al. (2017), instead, estimated FD using spherical harmonic reconstruction and observed an increase in FD in bipolar patients in the left lateral orbitofrontal cortex and right precuneus and a decrease in FD in the right caudal middle frontal, right entorhinal cortex, right pars orbitalis, left fusiform cortex and left posterior cingulate cortex (uncorrected).

3.4.3 | Depressive disorder

The only study that evaluated FD in patients with depressive disorder reported lower FD values of the right caudal middle frontal gyrus in patients with treatment-resistant depression than in HC (uncorrected) (Schmitgen et al., 2019). Schmitt et al. (2021) evaluated the association between polygenic risk scores (PRS) for depression

and FD values in healthy individuals and observed that genetic risk for depression was associated with cortical complexity in the right orbitofrontal cortex.

3.4.4 | Obsessive–compulsive disorder (OCD)

Only one of the retrieved studies analysed FD in patients with OCD (Tae et al., 2005). The authors estimated three-dimensional whole-brain and hemispheric FD and observed an overall reduction in FD in patients with OCD compared with HC.

3.4.5 | Eating disorders

Three of the retrieved studies analysed FD in patients with eating disorders (Cascino et al., 2020; Collantoni et al., 2020; Nickel et al., 2019). All included patients with acute anorexia nervosa (AN) and patients who recovered from AN, while only the study by Cascino et al. (2020) also included patients with bulimia nervosa (BN). Although one study did not find differences between groups (Cascino et al., 2020), the remaining two reported significant results.

Regarding the differences between patients with acute AN and HC, Collantoni et al. (2020) observed that patients with AN presented an overall reduction in FD, encompassing more than 20 cortical areas. Nickel et al. (2019), instead, reported a higher FD in patients with AN, compared with HC in the left precentral gyrus, and a reduction in FD in AN limited to the left middle occipital gyrus and the right middle frontal gyrus. Regarding patients recovered from AN, Nickel et al. found no significant differences between recovered patients and HC, while the study by Collantoni et al. reported higher FD in rec-AN than in HC in the left superior temporal sulcus and the left subcentral gyrus and sulcus and lower FD in rec-AN in the bilateral superior parietal lobule, left postcentral gyrus, right intraparietal sulcus and bilateral parieto-occipital sulci.

3.5 | Neurological disorders

3.5.1 | Alzheimer's disease (AD)

The four studies that evaluated FD in patients with AD reported an overall reduction in FD in these patients, compared with HCs (King et al., 2009, 2010; Nicastro et al., 2020; Ruiz de Miras et al., 2017). In particular, King et al. (2009) estimated the 2D FD of the cortical ribbon in four coronal and three axial images and observed that in six out of seven slices patients presented lower FD values than HCs. The same author also estimated the 3D FD of the pial surface, the GM–WM interface surface and the cortical ribbon and observed that the FD of the cortical ribbon and the GM–WM surface was lower in AD patients than in controls (King et al., 2010). The authors of the other two studies estimated FD using spherical harmonic reconstruction, and both observed a reduction in whole-brain FD in patients with AD (Nicastro et al., 2020; Ruiz de Miras et al., 2017). Regarding regional differences, both studies reported lower FD values in AD patients than in controls in regions that encompass the insula, the medial temporal lobe and the posterior cingulate cortex. Nicastro et al. (2020) also observed differences in FD between AD patients and HC in the precentral and postcentral gyri, while Ruiz de Miras et al. (2017) in the temporal pole.

Ruiz de Miras et al. (2017) also evaluated FD in patients with mild cognitive impairment (MCI) and discovered that MCI patients who would have converted to AD in the next 4 years displayed lower WM FD values than nonconverter MCI patients, especially in the medial frontal lobe. McDonough and Madan (2021), instead, estimated FD in individuals at risk for dementia, but without cognitive impairment, and observed no association between FD values and AD risk.

Lastly, correlation analyses revealed a positive association between FD values and cognitive performance, so that lower FD values were associated with higher cognitive impairments (King et al., 2010; Nicastro et al., 2020; Ruiz de Miras et al., 2017).

3.5.2 | Frontotemporal dementia (FTD)

One of the two studies evaluating FD in patients with FTD was conducted by Nicastro et al. (2020). The authors reported a reduction in FD in patients, as compared with HCs, both in whole-brain values and regionally in the insula, posterior cingulate cortex and precentral and postcentral gyri. Patients with FTD also had lower FD values in the bilateral orbitofrontal cortex, the left anterior insula and the paracentral gyrus compared with patients with AD. Lastly, correlation analyses revealed an association between memory, language and fluency impairment and reduced FD in the left insula, inferior temporal and medial orbitofrontal gyri. The global results were replicated by Sheelakumari et al. (2017) who analysed FD separately in two subtypes of FTD: behavioural variant FTD (bvFTD) and primary progressive aphasia (PPA). Compared with HC, both diagnoses were associated with a global reduction in cortical FD. Furthermore, while bvFTD appeared to be additionally characterized by low FD in the right hemisphere, in PPA, the reduction

affected the left hemisphere, hinting towards a link between this alteration and the behavioural manifestation of FTD. This was also supported by the finding of a negative correlation between the FD of the right hemisphere of bvFTD patients and their score on the frontal system behaviour scale, indicating that lower complexity is associated with a worse clinical status.

3.5.3 | Small vessel disease (SVD)

Only one of the retrieved studies evaluated differences in FD between HCs and patients with SVD and MCI (Pantoni et al., 2019). The authors estimated white and GM FD and observed a reduction in whole-brain WM FD in patients with SVD. Furthermore, they also observed a positive relationship between FD values and cognitive performance, so that a decrease in WM FD was associated with a worsening in cognitive performance.

3.5.4 | Epilepsy

Four of the retrieved studies evaluated FD in patients with epilepsy (Cook et al., 1995; Free et al., 1996; Z. Li, Zhang, Wang, et al., 2020; Lin et al., 2007). Cook et al. (1995) estimated the 2D FD of the GM–WM boundary in patients with frontal lobe epilepsy (FLE) and temporal lobe epilepsy (TLE), observing that 9 out of 16 patients with FLE had abnormal FD values, while none of the patients with TLE had abnormal FD values. Lin et al. (2007) also evaluated FD in patients with TLE. However, they estimated 3D cortex FD and observed reduced FD in patients with TLE, compared with HCs, in bilateral temporal and occipital regions and in the left parietal regions. Furthermore, patients with left TLE also showed reduced FD in the left frontal and right parietal regions.

The study by Free et al. (1996) reported FD abnormalities in patients with cryptogenic epilepsy. In particular, the authors estimated 3D FD of the WM surface and observed that 17 of 39 patients had abnormal FD values.

Lastly, Z. Li, Zhang, Wang, et al. (2020) evaluated FD in benign childhood epilepsy with centrotemporal spikes (BECTS) but did not observe significant differences in FD between patients and HC.

3.5.5 | Spinocerebellar ataxia (SCA)

Three of the retrieved studies analysed FD in patients with SCA (Huang et al., 2017; Marzi et al., 2018; Wang et al., 2015).

Two of these studies evaluated FD in patients with type 3 SCA using a 3D box-counting method, and both reported reduced cerebellar cortex FD in patients with SCA3, compared with HCs (Huang et al., 2017; Wang et al., 2015). Wang et al. (2015) also reported reduced cerebral cortex FD values in patients with SCA3 and observed significant negative correlations between cerebellar and cerebral cortex FD values and the duration of the disease and between cerebellar cortex FD and the severity of ataxia, evaluated using the Scale for Ataxia Assessment and Rating (SARA).

In the last study, Marzi et al. (2018) evaluated FD in patients with type 2 SCA and reported that cerebellar and cerebral GM and cerebellar WM FD values were significantly lower in patients with SCA2 than in controls.

3.5.6 | Amyotrophic lateral sclerosis (ALS)

Two of the retrieved studies evaluated FD in patients with ALS (J. H. Chen, Huang, et al., 2020; Rajagopalan & Pioro, 2021). J. H. Chen, Huang, et al. (2020) estimated the FD of 152 cortical regions using spherical harmonic reconstruction and observed lower FD values in patients with ALS, compared with HCs, in the left precentral gyrus and central sulcus, left circular insular sulcus (superior segment), left cingulate gyrus and sulcus (middle-posterior part), right precentral gyrus and right postcentral gyrus. Rajagopalan and Pioro (2021) evaluated FD in HCs and four subgroups of patients with ALS and observed reduced FD of the right primary motor cortex, the bilateral primary sensory cortex and the whole brain only in the subgroup of patients with ALS and FTD. Both studies evaluated the relationship between FD values and clinical variables. However, only J. H. Chen, Huang, et al. (2020) obtained significant results and observed a positive correlation between the FD of the right precentral gyrus and the scores of the revised ALS Functional Rating Scale (ALSFRS-R), a negative correlation between the FD of the right precentral gyrus and the rate of disease progression and a negative correlation between the FD of the left circular sulcus of the insula and the duration of the disease.

3.5.7 | Minimal hepatic encephalopathy

Only one study evaluated FD in patients with minimal hepatic encephalopathy (Q. F. Chen, Zhang, et al., 2020). The authors estimated FD using spherical harmonic reconstruction and observed reduced FD values in patients with minimal hepatic encephalopathy, compared with controls, in the bilateral pericalcarine cortex,

bilateral paracentral cortex, left precuneus, left supramarginal gyrus, right anterior caudal cingulate cortex, right isthmus cingulate cortex and right insula.

3.5.8 | Multiple sclerosis (MS)

We reviewed a study on MS, which was conducted by Esteban et al. (2009). The authors compared patients with MS with controls, also dividing patients between those who just had the first attack of MS (FAMS) and those who suffered from relapsing–remitting MS (RRMS). The study found that, overall, the MS group showed significantly higher whole-brain FD compared with HC and that specifically, at the RRMS stage of the disorder, the cortical complexity was higher than at the first episode. This suggests a relationship between the damage caused by MS attacks and an increase in FD, which was corroborated by the finding of a positive correlation between the complexity index and the lesion loads identified with both T1 and T2 MR images.

3.5.9 | Huntington's disease

Kubera, Schmitgen, Hirjak, et al. (2019) analysed FD in patients with premanifest Huntington's disease and observed lower FD values in patients than in HCs in the bilateral lingual gyrus, left supramarginal, postcentral and precentral cortex, right precuneus and right posterior and middle cingulate gyrus.

However, the patients also presented an area of increased FD that encompassed the middle and superior temporal cortex of the left hemisphere.

3.5.10 | Parkinson's disease

To date, only two studies have evaluated FD in patients with Parkinson's disease. The first (D. Li, Wang, et al., 2020) reported reduced FD values in patients in the left precentral and postcentral cortex, left superior frontal cortex, left caudal middle frontal cortex, bilateral superior parietal cortex and right superior temporal cortex. In addition, they also observed that a longer duration of the disease was associated with a lower FD in the left postcentral cortex. Instead, the second study (Kubera, Schmitgen, Nagel, et al., 2019) did not find any alteration of FD in association with Parkinson's disease, despite significant thinning of the cortex. However, it should be noted that the samples included in the latter article were relatively limited in number, which could have hindered the power of the analyses.

3.5.11 | Williams syndrome

Thompson et al. (2005) conducted the only study that evaluated FD in patients with Williams syndrome. The authors calculated the FD of the two hemispheres and observed higher FD values in patients compared with HCs.

3.5.12 | Dyslexia

Only one of the retrieved studies evaluated FD in children and adolescents with dyslexia, and the authors observed higher values of FD in the left hemisphere of girls with dyslexia, compared with control girls (Sandu, Specht, et al., 2008).

3.5.13 | Autism spectrum disorder (ASD)

The only study evaluating FD in children with autism was conducted by Zhao et al. (2018). The authors estimated the FD of the right and left cerebellar cortex in male children with autism and typically developing boys, and observed reduced FD values in the right cerebellar cortex of children with ASD. Furthermore, they reported a significant positive relationship in the ASD group between the FD values and the difference between performance and verbal IQ.

3.6 | Other disorders

3.6.1 | Non-syndromic lip and palate cleft (NSCLP)

Li, Zhang, Li, et al. (2020) analysed the FD values in patients with NSCLP before and after articulation rehabilitation. Their results show that, while there were no differences in FD between patients and controls before rehabilitation, after rehabilitation, patients showed reduced FD values in the right inferior parietal lobule.

3.6.2 | Very premature birth

Hedderich et al. (2020) analysed the differences in FD between very prematurely born and term-born individuals at the age of 26 years. Their results show that premature births show reduced FD in the bilateral medial parietal cortex, the bilateral lateral temporal cortex and the right frontal operculum and the occipitotemporal junction. The authors also observed a positive correlation

between FD of the medial parietal and right lateral temporal cortices and IQ in premature-born adults, so that a decrease in FD was associated with lower IQ scores.

Results of FD studies in clinical populations are summarized in Table 2.

4 | DISCUSSION

The present review has summarized a large and heterogeneous literature, examining the complexity of cortical structure in different experimental samples, both healthy and pathological.

The revision of studies conducted on healthy individuals evidenced the potential of the FD to characterize the changes in cortical morphology associated with brain development and aging.

During the foetal stages of development, cortical complexity appears to increase with gestational age, following a trend similar to that described for gyrification (Wu et al., 2009). However, in later phases, studies evaluating changes in FD during infancy and in the transition from infancy to adulthood are quite consistent in highlighting an inverse correlation between cortical complexity and age. In fact, only one study observed an increase in FD with age (Blanton et al., 2001), but its results may be due to suboptimal imaging acquisition protocols and a small sample size (Marzi et al., 2020). With regard to aging, the literature is even more homogeneous and agrees in identifying a reduction in FD over time. These findings are consistent with results obtained from studies assessing cortical complexity by means of different morphological indices, such as local GI (Hogstrom et al., 2013). However, possibly because it summarizes in a single index different aspects of cortical morphology, FD appears to be more strongly related to age than gyrification or cortical thickness, and thus could provide unique contribution to the understanding of brain developmental and aging processes (Madan & Kensinger, 2018).

Although the neural mechanisms underlying the observed decrease in cortical complexity are not clear yet, FD reduction could reflect the pruning process occurring during childhood and early adulthood, characterized by reduction in cells and connectivity, and the loss of dendrites, spines density and synapses observed in healthy aging (Marzi et al., 2020).

It is interesting to note that a reduction in FD appears to be associated not only with aging but also with reduced cognitive functioning. A negative correlation has been observed between FD values and cognitive performance in healthy individuals and patients with different neurological conditions, such as AD, FTD and SVD. This evidence, which appears to be quite robust among the examined studies, further supports the use of FD in the study of aging and different neurological and psychiatric diseases.

To date, many studies have already evaluated cortical complexity in clinical populations using FD.

Regarding psychiatric disorders, the prevalent disorders in FD literature is schizophrenia, but probably due to differences in recruitment criteria and methodologies, the results of these studies are quite heterogeneous. However, most of them showed a reduction in FD in schizophrenia patients compared with HCs. Furthermore, the only study showing an increase in FD in schizophrenia patients was conducted in a very small experimental sample and should therefore be interpreted with caution (Sandu, Rasmussen, et al., 2008).

So far, few studies have been conducted on other psychiatric disorders. The results are limited and heterogeneous, but almost all studies reported the presence of global or regional FD alterations in the clinical population, suggesting the importance of further including this parameter in the neurobiological evaluation of these conditions. Moreover, it could also be useful to look at transdiagnostic alterations in FD, because they can provide evidence of different neurobiological substrates in disorders with a common clinical symptomatology, such as schizophrenia and bipolar disorder (Trevisan et al., 2022).

Interestingly, a study that evaluated cortical complexity in a sample of patients with AN found that FD was reduced in the clinical sample compared with HCs and was inversely associated with BMI, suggesting a potential usefulness of this cortical index in evaluating the effect of malnutrition on brain structure (Collantoni et al., 2020).

Regarding neurological disorders, the literature is quite homogeneous in reporting reduced FD values in patients suffering from various neurodegenerative disorders, including AD, FTD, Parkinson's disease, SCA and ALS. The only exception appears to be represented by patients suffering from MS, who showed an increase in FD, probably related to the presence of inflammatory components and cellular changes in GM (Esteban et al., 2009).

An interesting approach regarding the use of FD in the field of neurodegenerative disorders concerns the possibility of detecting structural alterations in the early stages of the disease. Although only few studies addressed this issue, alterations in cortical complexity have already been observed in patients with MCI who would have converted to AD and in patients with premanifest Huntington's disease (Kubera, Schmitgen, Hirjak, et al., 2019; Ruiz de Miras et al., 2017). A further potential of this index, which results from various studies (King et al., 2010; Nicastro et al., 2020; Sheelakumari et al., 2017), could be found in the direct association between its alteration and the clinical worsening

TABLE 2 Synthesis of the systematic review main findings on clinical populations

Disorder	No. of studies	Main findings
Alzheimer's disease	4	Lower FD in patients with Alzheimer's disease than in HC
Amyotrophic lateral sclerosis	2	Areas of lower FD in patients with amyotrophic lateral sclerosis than in HC
Anorexia nervosa	3	Mixed results: 1 study reported no differences between patients with anorexia nervosa and HC, 1 study reported lower FD in patients than in HC and 1 study reported areas of both increased and decreased FD in patients, compared with HC
Autism	1	Lower R cerebellar FD in patients with autism than in HC
Benign childhood epilepsy	1	No differences in FD between patients and HC
Bipolar disorder	3	Mixed results: 1 study reported higher FD in patients than in HC, 1 study reported lower FD in patients than in HC and 1 study reported areas of both increased and decreased FD in patients with bipolar disorder, compared with HC
Bulimia nervosa	1	No differences in FD between patients with BN and HC
Cryptogenic epilepsy	1	Abnormal FD values in patients with cryptogenic epilepsy
Dyslexia	1	Higher FD of the L hemisphere in girls with dyslexia than in HC girls
Frontal lobe epilepsy	1	Abnormal FD values in patients with frontal lobe epilepsy
Frontotemporal dementia	2	Lower FD in patients with frontotemporal dementia than in HC
Huntington's disease	1	Areas of both increased and decreased FD in patients with premanifest Huntington's disease
Minimal hepatic encephalopathy	1	Areas of lower FD in patients with minimal hepatic encephalopathy than in HC
Multiple sclerosis	1	Higher FD in patients with multiple sclerosis than in HC
Obsessive compulsive disorder	1	Lower FD in patients with obsessive compulsive disorder than in HC
Parkinson's disease	2	Mixed results: 1 study reported areas of lower FD in patients with Parkinson's disease than in HC, while 1 study reported no differences between patients and HC

(Continues)

TABLE 2 (Continued)

Disorder	No. of studies	Main findings
Schizophrenia	7	Mixed results: 1 study reported higher FD in patients with schizophrenia than in HC, 2 studies reported no differences between patients and HC and 4 studies reported lower FD in patients than in HC
Small vessel disease	1	Lower FD in patients with small vessel disease than in HC
Spinocerebellar ataxia	3	Lower cerebral and cerebellar FD in patients with spinocerebellar ataxia than in HC
Temporal lobe epilepsy	2	Mixed results: 1 study reported no differences in FD between patients with temporal lobe epilepsy and HC, while 1 study reported areas of lower FD in patients than in HC
Treatment-resistant depression	1	Lower FD in patients with depression than in HC in the R caudal middle frontal gyrus
Williams syndrome	1	Higher FD in patients with Williams syndrome than in HC

associated with a specific disorder. Therefore, future research should take into account the opportunity to evaluate the association between cortical complexity and specific clinical parameters.

Studies on other neurological disorders are too few to draw conclusions. However, there is evidence of areas of increased FD in patients with William syndrome and girls with dyslexia and decreased FD in patients with ASD and minimal liver encephalopathy.

The main limitation of this paper is inherent in the heterogeneity of the considered research field, which prevents the possibility of meta-analysing the data, even of specific subpopulations, and which makes the discussion of this topic somewhat broad and complex. The present review highlighted three main sources of heterogeneity, related to study objectives, sample selections and the different methodologies used to compute the fractal dimension. In fact, methodological differences between studies make it difficult to compare their results, even when obtained in homogeneous clinical or nonclinical samples. Future research should evaluate the reliability of the different methods used to compute FD and should also aim to better specify which computational technique would be the most appropriate for specific research questions.

In conclusion, this largest and most comprehensive review of the use of FD to describe cortical complexity in healthy and clinical populations confirms the usefulness of this index in describing specific cortical characteristics, as well as its sensitivity to detect morphological modifications related to developmental or pathological processes. FD appears to be particularly useful in capturing additional morphological information to that described by other cortical indices such as cortical thickness, local GI and cortical surface and should therefore be used more systematically in the structural evaluation of the cortex. Finally, the present review evidenced a lack of longitudinal observations in the existing FD literature, which appear however very important to better understand the role of cortical complexity in different neurodevelopmental phases and aging. Further longitudinal observations employing FD to characterize the cortical structure are therefore needed.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any financial or commercial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTION

The study was conceptualized by EC, FA and VM. Paper selection and data extraction were carried out by AM, EC, FA, NT, PM and VM. The paper was written by EC, FA and VM with the supervision of AF, CRM and FS. All authors approved of the final version.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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