RESEARCH ARTICLE

Network-based decoupling of local gyrification in obsessive-compulsive disorder

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Abstract

Gyrification is associated with cortical maturation and closely linked to neurodevelopmental processes. Obsessive-compulsive disorder has previously been associated with neurodevelopmental risk factors. Using graph theoretical modeling we examined structural covariance patterns to assess potential disruptions in processes associated with neurodevelopment in OCD. In total 97 patients and 92 healthy controls underwent magnetic resonance imaging. Structural covariance networks based on local gyrification indices were constructed using an atlas-based parcellation scheme. Network properties were assessed using the network-based statistic as well as global and local graph theoretical measures. Correlations between gyrification and symptom severity as well as age of disease onset were examined. Network-based statistic analysis revealed one cluster with significantly decreased structural covariance in patients comprising mainly ventral brain regions ($p = .041$). Normalized characteristic path length was found to be impaired in patients ($p = .051$). On a nodal level, left middle frontal sulcus displayed a significantly decreased local clustering coefficient ($p < .001$). Finally, gyrification in several inferior frontal nodes significantly correlated with age of onset but not symptom severity. The decrease in a gyrification-based covariance network in OCD appears to be mostly confined to ventral areas in which gyrification starts the latest during development. This pattern may indicate that alterations taking place during development are potentially time locked to specific periods. Correlations between gyrification in inferior-frontal nodes and age of onset potentially indicate a structural trait rather than state marker for OCD. Finally, a trend in impaired global integration capabilities may point towards potentially widespread global alterations during neurodevelopment in patients.

KEYWORDS

connectome, gyrification, MRI, network, OCD

1 | INTRODUCTION

The processes leading to the characteristic differentiation of the brain's surface into sulci and gyri, called gyrification, have been studied across

various species employing a broad range of experimental techniques (Zilles, Palomero-Gallagher, & Amunts, 2013). Different theoretical accounts have been put forward to explain gyrification (Fernandez, Llinas-Benadero, & Borrell, 2016; Ronan & Fletcher, 2015; Sun & Hevner, 2014) with a common assumption that it increases efficiency regarding metabolic cost via shorter axons and thus increased information processing speed (Striedter, Srinivasan, & Monuki, 2015; White, Su, Schmidt, Kao, & Sapiro, 2010). Further evidence also indicates a potential relationship between structural connectivity and cortical folding (Takahashi, Folkerth, Galaburda, & Grant, 2012; Van Essen, 1997). Additionally, several studies have revealed a structure-cognition

Abbreviations: FDR, false discovery rate; HC, healthy controls; IGI, local gyrification index; NaSSA, noradrenergic and specific serotonergic antidepressant; NBS, network-based statistic; NDRI, norepinephrine-dopamine reuptake inhibitor; OCD, obsessive-compulsive disorder; SSRI, selective serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

relationship in healthy subjects in terms of associations between local gyrification and cognitive performance in working memory and mental flexibility tasks (Gautam, Anstey, Wen, Sachdev, & Cherbuin, 2015) as well as attention and semantic verbal fluency tasks (Jockwitz et al., 2017). Interestingly, gyrification has been demonstrated to mainly occur between the last two trimesters of gestation up to approximately one year (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995; White et al., 2010), thus making it a potential marker for early neurodevelopment. In line with the fact that gyrification is clearly associated with neurodevelopment, there has been accumulating evidence of alterations in diseases featuring a neurodevelopmental component such as autism spectrum disorder (Ecker et al., 2016), depression (Han et al., 2017) and schizophrenia (Palaniyappan & Liddle, 2012; Palaniyappan et al., 2016; Palaniyappan, Park, Balain, Dangi, & Liddle, 2015). Recent evidence points towards altered gyrification patterns to be also found in obsessive-compulsive disorder (OCD) which has previously been discussed as a disorder with neurodevelopmental risk factors (Huyser, Veltman, de Haan, & Boer, 2009; Rosenberg & Keshavan, 1998). However, results regarding alterations in cortical folding in OCD are somewhat heterogeneous with the majority of studies reporting hypogyrfication (Rus et al., 2016; Shim et al., 2009; Wobrock et al., 2010) or gender-specific hypogyrfication (Venkatasubramanian et al., 2012), and others reporting hypergyrfication (Fan et al., 2013). Thus far, analyses of gyrification patterns were typically based on univariate (i.e., region of interest) or mass-univariate (e.g., whole-brain, vertex-wise) approaches yielding information on local changes. While being entirely valid in their own right, it has recently become feasible to additionally infer information at a network level employing connectomics-based methods. Here, the focus is shifted from observing purely local differences towards observing changes in the covariance between morphological properties within brain regions (Alexander-Bloch, Giedd, & Bullmore, 2013). Thus far, the evaluation of structural as well as functional brain alterations employing a network level perspective has revealed important new results that have the potential to further inform neurobiological models of OCD by providing additional information on disease specific alterations in selected parameters of network complexity (Feusner et al., 2015; Jung et al., 2017; Moreira et al., 2017; Reess et al., 2016; Shin et al., 2014; Vaghi et al., 2017). To date numerous studies of anatomical covariance based networks (mainly using measures of cortical thickness or volume) have been conducted (Evans, 2013) and first studies of gyrification-based networks in schizophrenia have recently been published (Palaniyappan et al., 2016; Palaniyappan et al., 2015). The aim of our study is to extend recent local findings of altered gyrification in OCD to the network level, via examination of gyrification-based covariance networks. To this end we based our analysis on data previously described in Rus et al. (Rus et al., 2016) but further increased the sample size by adding an independent set of another 42 subjects (OCD = 24, healthy controls = 18) resulting in total sample sizes of $n = 97$ patients and $n = 92$ healthy controls. To the best of our knowledge, to date no study has examined gyrification-based networks in OCD employing a connectomics approach. Given the previously described alterations found in local measures of gyrification, it seems likely to also find changes in structural covariance on the

network level. However, this is not a necessity since differences in gyrification derived from local examination do not have to map closely to differences derived from network analyses examining covariance between regions, and vice versa. We therefore propose two alternative scenarios regarding the results. The absence of alterations in gyrification-based networks regarding global topological measures might speak in favor of changes that are locally confined (i.e., hardly tractable by assessing global network measures), and may thus be interpreted as potentially independent in mechanism, therefore resulting in rather focal changes. Alternatively, alterations in global network topology may be indicative of impairments in the development of the system as a whole. More specifically, changes in measures of segregation might be indicative of developmental changes on a modular level, whereas changes in measures of integration might point towards a potentially common mechanism affecting neurodevelopment on a rather global level and/or time span. A second line of questioning addresses potential relationships between gyrification and the age of disease onset as well as symptom severity. Correlations with age of onset may further point towards altered gyrification being a neurodevelopmental risk factor in OCD.

2 | MATERIALS AND METHODS

2.1 | Participants

The study sample comprised three different samples examined at two centers. A total of $n = 97$ patients with OCD as the primary diagnosis were included in the study. Patients of two samples (M1_ocr, $n = 39$; M2_ocr, $n = 25$), both scanned at the Klinikum rechts der Isar, Technische Universität München, Germany were recruited from the Windach Institute and Hospital of Neurobehavioral Research and Therapy (WINTR), an institution specialized in the treatment of OCD. The third sample (J1_ocr, $n = 33$) was recruited and scanned at the University Hospital for Psychiatry and Psychotherapy, Jena, Germany. All subjects were in-house patients, diagnosed by an experienced psychiatrist according to DSM-IV criteria. As a control group $n = 92$ age and gender-matched healthy subjects were included (M1_hc, $n = 41$; M2_hc, $n = 19$; J1_hc, $n = 32$). Exclusion criteria for all subjects were a history of clinically important head injuries, seizures or neurological diseases. There were no significant differences between healthy controls and OCD patients regarding age (two-sample t test, two-tailed; $t_{187} = -0.667$, $p = .505$) and gender (Chi-Square test; $\chi^2_{102} = 107.79$, $p = .281$). For demographical and clinical sample characteristics, see Table 1.

At the time of the study, $n = 36$ patients were drug-naïve or medication free for at least 3 weeks. No patients were excluded due to comorbidities and $n = 30$ patients had one or more comorbid diagnosis. Prior to scanning, patients were handed the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) to assess clinical severity of obsessive-compulsive symptoms. The study was approved by the local Ethics Committee of the Klinikum rechts der Isar, München and the Ethics Committee of the University Hospital Jena. The study protocol was in compliance with the Declaration of Helsinki.

TABLE 1 Demographic and clinical sample characteristics

Characteristics	OCD (n = 97) n (%) or mean $\pm$ SD (range)	HC (n = 92) n (%) or mean $\pm$ SD (range)
Female	65 (67.0%)	54 (58.7%)
age (years)	32.5 $\pm$ 9.1 (19–62)	30.2 $\pm$ 9.6 (18–57)
age of onset	17.3 $\pm$ 6.4	–
Y-BOCS total	20.9 $\pm$ 6.2 (9–38)	–
Obsession	10.5 $\pm$ 4.0 (0–20)	–
Compulsions	10.6 $\pm$ 3.5 (0–19)	–
comorbidities	31 (32.0%)	–
depression	21	–
anxiety disorders	10	–
personality disorder	4	–
eating disorder	2	–
ADHD	2	–
medication	56 (57.7%)	–
SSRI	43	–
SSNRI	8	–
neuroleptic	5	–
TCA	4	–
methylphenidate	2	–
benzodiazepine	1	–
NDRI	1	–
NaSSA	1	–

Note that multiple comorbid diagnosis as well as different medication types can be present in a single patient.

Abbreviations: HC, healthy controls; NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI, norepinephrine-dopamine reuptake inhibitor; OCD, obsessive-compulsive disorder; SSNRI, selective serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

2.2 | Image acquisition

Structural magnetic resonance imaging (MRI) at the Munich site was conducted on a 3T Philips Ingenia (Philips Healthcare, Best, The Netherlands) using a 12-channel (SENSE) head coil (M1_ocrd, M1_hc) or a 32-channel (SENSE) head coil (M2_ocrd, M2_hc). MRI at the Jena site was conducted on a 3T Siemens MAGNETOM (Siemens Medical Solutions, Erlangen, Germany) using a 12-channel receive-only head matrix coil (J1_ocrd, J1_hc). Details regarding image acquisition parameters are given in the Supporting Information.

2.3 | Image processing

Cortical surface reconstruction was conducted using FreeSurfer's (V5.3.0 <http://surfer.nmr.mgh.harvard.edu/>) standard processing pipeline (Dale, Fischl, & Sereno, 1999; Fischl et al., 2002; Fischl, Sereno, & Dale, 1999). After reconstruction, local Gyrification Index (IGI) was computed based on the method developed by Schaer et al. (2008). In

short, the algorithm provides a ratio between the pial surface area and cortical sheet surface area, sampled over regions of interest that are spread over cortex. This approach results in a continuous vertex-based measure of local gyrification index over the entire cortical surface. For subsequent graph construction, FreeSurfer's Destrieux brain parcellation scheme was applied (Destrieux, Fischl, Dale, & Halgren, 2010) and all reconstructed brain data were parcellated accordingly yielding a total of 74 regions within each hemisphere. Quality control was performed using the ENIGMA cortical quality control protocols (<http://enigma.ini.usc.edu/protocols/imaging-protocols/>). Destrieux based parcellations were additionally overlaid on reconstructed surfaces and visually checked after running the QA Tools provided on the FreeSurfer webpage (<https://surfer.nmr.mgh.harvard.edu/fswiki/QATools>).

2.4 | Graph construction

In a first step, the averaged IGI values within each parcellated brain region were adjusted for age, sex, scan sequence, and total intracranial volume using multiple regression in line with He, Chen, and Evans, (2007). The residuals were subsequently used as a proxy for subjects' IGI. Each brain region derived from the Destrieux parcellation was assigned as a node. An edge represented the correlation between the adjusted IGIs of two nodes. Correlations for every possible pair of nodes (N_i, N_j) were computed, resulting in a 148×148 symmetric graph, representing a gyrification-based structural covariance network. To avoid the influence of spurious relationships, significance of correlations was tested and only edges surviving FDR-correction ($p < .05$) were retained. Subsequently, to perform network analysis, a graph was constructed for each group (i.e., OCD patients and healthy controls) and all edges previously identified as exceeding the FDR-corrected threshold were set to zero. These FDR-corrected correlation matrices were subsequently used to conduct a network-based statistic (NBS) analysis. For computation of graph measures the connectivity matrices were thresholded over a range of connection densities (see Graph theoretical analysis below) in order to preserve the same number of edges in each group.

2.5 | Network-based statistic analysis

Group differences between IGI based networks were examined using the framework of the NBS introduced by Zalesky et al. (Zalesky, Fornito, & Bullmore, 2010). NBS is a nonparametrical method to deal with the multiple comparison problem encountered in conducting mass univariate significance testing in graphs. Statistical significance is established for specific subsets of nodes that are mutually connected in topological rather than physical space. The first step requires the computation of a test statistic, in this case the difference in Fishers z-transformed group-based correlation coefficients. Second, a primary component forming threshold ($p < .001$, two sided test) is applied to identify all edges displaying potential differences in IGI correlations. Third, all subthreshold edges are assessed for mutual connections forming clusters in topological space that may point towards the existence of non-chance clusters. Permutation testing is then applied to

compute p values for every component previously identified. For each of 10,000 permutations, group labels are randomly shuffled resulting in two new groups with sample sizes being equal to the original groups. Within each, correlation coefficients between nodes are determined and subsequently Fisher z -transformed. For each edge the difference in z -transformed correlation coefficients between groups is computed. Based on these matrices steps two and three are repeated with noting the maximum cluster size of components resulting in a null distribution for largest component size. The final hypothesis test is then carried out for the empirically determined components by comparing their sizes with the proportion of permutations yielding a component with equal or greater size. The final result controls the family-wise error rate at cluster level with $p < .05$. Visualization of NBS networks was conducted using BrainNet Viewer (V1.53; Xia, Wang, & He, 2013).

2.6 | Graph theoretical analysis

The following global graph measures were computed: normalized average clustering coefficient γ to assess segregation, as well as normalized average path length λ to assess integration. Finally sigma ($\sigma = \frac{\gamma}{\lambda}$) was used as an index of small-worldness. Normalization of network measures was based on dividing the empirically found measure by the respective measure computed over a total of 1,000 null networks created using a rewiring algorithm that preserves the degree distribution. As a local measure of segregation, node-based normalized local clustering coefficients were computed. As a local measure of integration, node-based normalized local efficiencies were computed. Statistical comparisons for all measures were based on permutation testing with 1,000 permutations. Subject data was randomly sampled and assigned to a group while preserving the original group sizes (healthy controls and OCD). For each resampling, the resulting correlation matrices were binarized and thresholded. As the computation of graph measures is strongly influenced by fragmented connectivity matrices (Fornito, Zalesky, & Bullmore, 2016) the measures were computed for a range of densities (0.1–0.5 with increments of 0.05) over which no fragmentation of graphs occurred. Subsequently, the empirically found group differences for global and local graph measures were compared with the distribution of group differences constructed from computing the graph measures across all resampled connectivity matrices. Computing each measure over the given range of densities results in a curve for each measure that is finally compared between groups over the entire threshold range using functional data analysis (Ramsay, 2005), effectively accounting for the multiple comparison problem. Simultaneously taking into account the values over the entire threshold range effectively avoids the multiple comparison problem typically encountered if comparing the differences over various density values. All results were tested at $p < .05$ based on a two-sided test. For local graph measures, results are reported at $p < .05$, using FDR-correction. For formulas regarding the computation of network measure see Rubinov & Sporns (Rubinov & Sporns, 2010). All measures were calculated on the group based connectivity matrices using the Graph Analysis Toolbox (GAT, V1.3.32; Hosseini, Hoeft, & Kesler, 2012) which draws

on algorithms provided in the Brain Connectivity Toolbox (BCT) using Matlab (R2013a, The MathWorks, Inc., Natick, MA).

2.7 | Correlations with clinical scores

Potential relationships between clinically relevant information (Y-BOCS, age of onset) and node-based IGIs were assessed using Pearson correlation coefficients based on data adjusted for age, sex, scanner, and total intracranial volume. All correlations were corrected for multiple comparisons using FDR-correction at $p < .05$.

2.7.1 | Assessment for group x age interaction effects

Several studies have revealed differential age trajectories for structural brain measures such as cortical thickness (Fouche et al., 2017) and volume (de Wit et al., 2014) between OCD patients and healthy controls. To examine whether similar effects are present in the current sample, a separate model assessing group x age interaction effects, controlling for sex, total intracranial volume, as well as scan sequence was computed.

2.7.2 | Exploratory subgroup analyses

In order to assess potential effects of medication and comorbidity, exploratory subgroup analyses were performed. To this end, the patient group was split into patients with and without medication as well as with and without comorbidity. Subsequently, three comparisons for medication effects as well as for effects of comorbidity were conducted: (1) between patient groups only, (2) patients with medication or comorbidity vs. healthy controls, and (3) patients without medication or comorbidity versus healthy controls. Subgroup analyses comprised NBS as well as graph measures. We additionally performed NBS analyses to evaluate the influence of early versus late onset by splitting the patient sample using various thresholds (for details see Supporting Information).

3 | RESULTS

3.1 | NBS of gyrification based network alterations in OCD

NBS analysis revealed a single network of consistently reduced structural covariances in OCD patients as compared with healthy controls ($p = .041$, corrected, see Figure 1). The network comprised a total of 31 nodes (see Table 2) connected by 34 edges (see Table 3) and was distributed throughout both hemispheres (see Figure 1).

3.2 | Graph measures describing global and local network properties

Networks of both groups were found to be in the small-world regime indicated by γ -values > 1 and λ -values ~ 1 with σ exceeding one (see Table 4). No significant differences were found for σ as well as γ . However, the normalized average characteristic path length (λ) was different between groups at trend level ($p = .0510$) with OCD patients displaying a higher λ compared with healthy controls. For plots of group differences for each graph measure as a function of density see Figure 2.

FIGURE 1 Network-based statistic analysis results. Visualization of the significantly altered gyrification-based structural covariance network (i.e., decreased covariance) in OCD based on network-based statistic analysis ($p = .041$). Red dots indicate nodes comprising the cluster, gray lines indicate edges between nodes [Color figure can be viewed at wileyonlinelibrary.com]

3.3 | Local measures

A significant decrease in local clustering within left middle frontal sulcus was found in patients ($p < .001$, corrected). No significant differences were found for any other nodes regarding local clustering or local efficiency measures.

3.4 | Correlations with clinical scores

A total of five nodes revealed significant correlations (FDR-corrected) between IGI values and age of onset (see Table 5 and Supporting Information Table S1 for correlations at $p < .05$, uncorrected). All correlations were positive indicating that later age of onset was associated with larger IGIs. There were no significant correlations between IGI values and YBOCS-scores for any of the nodes in question.

3.5 | Group $\times$ age interaction effects

While age was significantly correlated with IGI values across widespread areas within each group separately (see Supporting Information Figure S1), there were no group $\times$ age interaction effects within the current sample.

3.6 | Exploratory subgroup analyses

3.6.1 | Effects of medication, comorbidity, and early versus late onset

There were no significant differences between medicated and unmedicated patients in the NBS analysis ($p = .199$). Comparison of medicated

patients vs. healthy controls ($p = .116$) as well as unmedicated patients versus healthy controls ($p = .799$) did not yield significant differences. There were no significant differences between patients with and without comorbidity ($p = .930$). Comparison of patients with comorbidity versus healthy controls ($p = .189$) as well as without comorbidities versus healthy controls ($p = .213$) did not yield significant differences. There were also no significant differences in NBS results regarding early versus late onset splits (see Supporting Information for more details).

4 | DISCUSSION

The current study reports on structural connectome differences in gyrification-based covariance networks between OCD patients and healthy controls. The results can be broadly split into three aspects: (1) NBS results assessing differences in the overall topology of the networks, (2) results from graph measures assessing differences in global as well as local characteristics in network structure, and (3) relationships between gyrification and the age of onset. Firstly, applying the framework of the NBS, one cluster with consistently decreased structural coupling in gyrification was identified in OCD. A striking feature in the pattern of this cluster is the asymmetry of decreased structural covariances towards rather ventral brain regions. More precisely, nodes found within the cluster can be broadly assigned to three categories: (a) inferior-frontal as well as (b) occipito-temporal regions, together accounting for $\sim 80\%$ of all nodes, and c) parieto-occipital regions in conjunction with parts of insula accounting for the remaining $\sim 20\%$ of nodes in the cluster. Interestingly, in OCD patients, Kim, Jung, Kim,

TABLE 2 Nodes comprising the significantly different network-based statistic cluster in obsessive-compulsive disorder

Region	Node	Left	Right
Inferior-frontal	Orbital sulci	×	×
	Gyrus rectus	×	
	Medial orbital sulcus	×	
	Suborbital sulcus	×	
	Orbital gyrus		×
	Lateral orbital sulcus		×
	Horizontal ramus of ant. segment of lateral sulcus		×
Occipito-temporal	Cuneus	×	×
	Lateral occipito-temporal gyrus	×	×
	Parahippocampal gyrus	×	×
	Lateral occipito-temporal sulcus	×	×
	Lingual gyrus	×	
	Middle occipital gyrus	×	
	Middle temporal gyrus	×	
	Superior temporal sulcus	×	
	Medial occipito-temporal sulcus and lingual sulcus	×	
	Anterior transverse collateral sulcus	×	
	Calcarine sulcus	×	
	Inferior temporal gyrus		×
Parietal	Precuneus	×	×
	Subparietal sulcus		×
Parieto-occipital	Parieto-occipital sulcus	×	×
Fronto-parietal	Central sulcus		×
Insula	Long insular gyrus and central sulcus of the insula	×	

Jang, and Kwon, (2013) found measures of nodal efficiency to be decreased in ventral and increased in dorsal nodes of brain networks constructed on the basis of cortical thickness. However, results are not directly comparable as it was demonstrated by Gautam et al. (2015) that cortical thickness and gyrification are typically negatively correlated in a rather unspecific, largely distributed pattern with the exception of aspects of medial frontal regions that are also negatively correlated but cover a rather large area and are more pattern-like.

Additionally, local measures of efficiency are computed on a nodal basis and are related to clustering coefficients. Nevertheless, first evidence from Kim et al. (2013) indicates alterations that are following a dorsal/ventral gradient. Our findings also point to a dorsal/ventral imbalance based on another anatomical measure, that is, gyrification covariance networks. Typically, an imbalance in dorsal/ventral fronto-striatal circuitry appears to be associated especially with cognitive inflexibility (Gu et al., 2008), with reduced dorsal circuit activity leading to disinhibition and thus increased activity in ventral fronto-striatal circuits. Additionally, ventral fronto-striatal circuits have been associated especially with altered reward processing and the regulation of affect in OCD (Milad & Rauch, 2012). There is accumulating evidence that networks constructed on the basis of structural covariance, that is, cortical thickness as well as gray matter volume, are indicating synchronized developmental changes (Alexander-Bloch et al., 2013; Khundrakpam et al., 2013; Zielinski, Gennatas, Zhou, and Seeley, 2010). Regarding the developmental trajectory of gyrification, it has been proposed that its starting point lies within dorsal parieto-occipital areas and over the course of development proceeds to *superior* frontal and temporal regions before finally continuing to *inferior* frontal and temporal regions (Takahashi et al., 2012). The spatial pattern of differences found in the NBS analysis might be indicative of an impairment that may be time locked to late stages in neurodevelopment as most of the affected nodes are located in inferior frontal and inferior temporo-occipital areas in which gyrification starts latest. Therefore, these ventrally located alterations in gyrification-based covariance networks in OCD patients may potentially be attributable to a common, yet still unknown, mechanism or cause related to a rather late period in neurodevelopment and may indicate a risk factor for the development of OCD. A similar pattern of alterations in grey matter volumes of mostly ventrally located brain regions such as the thalamus, hippocampus, OFC, posterior cingulate cortex and centrum semiovale can be observed in preterm birth (Ball et al., 2012). Additionally, there appears to be an overlap between grey matter alterations of ventral brain structures and associated intrinsic connectivity in preterm born adults as well (Bauml et al., 2015). Surprisingly, two recent studies have identified preterm birth and low birth weight (among others) to be risk factors for developing OCD (Brander et al., 2016; Fevang, Hysing, Markestad, & Sommerfelt, 2016). Given that IGI values for nodes did not correlate with symptom severity, alterations may potentially be interpreted as a trait instead of state marker in line with the notion of gyrification being a measure that is rather stable over time and revealed no group x age interaction effects in our sample. One striking feature, further illustrating the value of connectome based approaches in general, is the difference in results between the current study and the findings presented by Rus et al. (2016). Though in both studies the measure being analyzed is IGI, findings are somewhat different. Rus et al. (2016) report alterations mainly in insula and dorsal regions (i.e. inferior and superior parietal, post- and precentral as well as superior frontal areas) that are confined to the right hemisphere without revealing significant differences concentrating on ventral regions. This discrepancy in finding is, however, not surprising as both analyses essentially measure something potentially very different. In one case, it

TABLE 3 Edges comprising the significantly different NBS cluster in obsessive-compulsive disorder

Side	Edge connecting	
Left-left	Long insular gyrus/central sulcus of the insula	Parahippocampal gyrus
	Lateral occipito-temporal gyrus	Middle temporal gyrus
	Long insular gyrus/central sulcus of the insula	Calcarine sulcus
	Middle temporal gyrus	Med. occipito-temporal sulcus/lingual sulcus
	Cuneus	Orbital sulci
	Lingual gyrus	Orbital sulci
	Precuneus	Orbital sulci
	Calcarine sulcus	Orbital sulci
	Parieto-occipital sulcus	Orbital sulci
	Anterior transverse collateral sulcus	Suborbital sulcus
	Long insular gyrus/central sulcus of the insula	Superior temporal sulcus
	Lateral occipito-temporal gyrus	Superior temporal sulcus
	Parahippocampal gyrus	Superior temporal sulcus
	Med. occipito-temporal sulcus/lingual sulcus	Superior temporal sulcus
	Medial orbital sulcus	Superior temporal sulcus
Left-right	Medial orbital sulcus	Cuneus
	Gyrus rectus	Precuneus
	Medial orbital sulcus	Precuneus
	Suborbital sulcus	Precuneus
	Parahippocampal gyrus	Horiz. ramus of ant. segment of lateral sulcus
	Middle temporal gyrus	Central sulcus
	Middle occipital gyrus	Lateral occipito-temporal sulcus
	Lateral occipito-temporal sulcus	Orbital sulci
	Medial orbital sulcus	Parieto-occipital sulcus
right-right	Long insular gyrus/central sulcus of the insula	Subparietal sulcus
	Lateral occipito-temporal gyrus	Orbital gyrus
	Parahippocampal gyrus	Lateral occipito-temporal sulcus
	Orbital gyrus	Lateral occipito-temporal sulcus
	Precuneus	Lateral orbital sulcus
	Lateral occipito-temporal gyrus	Orbital sulci
	Inferior temporal gyrus	Orbital sulci
	Lateral occipito-temporal sulcus	Orbital sulci
	Lateral orbital sulcus	Parieto-occipital sulcus
	Orbital sulci	Parieto-occipital sulcus

is a vertex-by-vertex comparison of IGI between groups while in the other case it is the comparison of mutual correlation between IGI of different brain regions between groups. However, there is also some overlap regarding correlations with age at onset. Comparing the correlation between IGI and age at onset reported in Rus et al. (2016) with correlations between average node-wise IGI with age at onset from the current study reveals a substantial overlap. It should be kept in mind,

however, that correlations in the current study are significantly correlated at an uncorrected threshold of $p < .05$ which, on the other hand, is likely due to the need for multiple comparison adjustment which in case of network based studies is typically quite extensive. Finally, the overlap in correlations is not surprising as a large proportion of the sample is essentially based on the same subjects. Secondly, the overall network topology assessed by measuring small-worldness showed no

TABLE 4 Global topological measures of gyrification-based structural covariance networks

	Healthy controls	Obsessive-compulsive disorder	Functional data analysis based permutation test (<i>p</i> values)
Small-world index (σ)	1.5019 (0.5029)	1.6104 (0.4589)	0.5480
Normalized average clustering coefficient gamma (γ)	1.6492 (0.7182)	1.8363 (0.7910)	0.3460
Normalized average characteristic path length (λ)	1.0730 (0.0847)	1.1060 (0.1371)	0.0510

All indices mean $\pm$ SD.

significant abnormalities in patients. This finding is in line with other studies employing graph based analysis strategies in schizophrenia using gyrification based networks (Palaniyappan et al., 2016; Palaniyappan et al., 2015) as well as various other structural outcome measures in OCD (Kim et al., 2013; Reess et al., 2016; Zhong et al., 2014). However, the normalized average characteristic path length (λ) was found to be decreased in patients at trend level ($p = .051$) potentially indicating a decreased global integration capability in patients. Considering that nodes within the impaired network found using NBS analysis are mainly distributed ventrally, one might try to probe whether the trend effect in normalized average characteristic path length is mainly driven by alterations between ventral nodes. This type of analysis would

however be circular if conducted within the same data set. The only node displaying significant differences (FDR-corrected) regarding local clustering was found to be the left middle frontal sulcus. In OCD, this node's clustering coefficient was decreased, indicating that its topological neighbors are less well connected with each other than in healthy controls. This is a potentially relevant finding given the anatomy and functionality of the middle frontal sulcus. The middle frontal sulcus is buried within middle frontal gyrus (Destrieux et al., 2010) and overlaps with dorso-lateral prefrontal cortex (DLPFC), a region that has previously been associated with planning abilities. Interestingly, van den Heuvel et al. (2005) report a decreased activity in left DLPFC-striatal responsiveness in obsessive compulsive disorder to go along with

FIGURE 2 Global graph-measures as a function of density. (a) Between-group differences in normalized average clustering coefficients, γ . (b) Between-group differences in normalized average characteristic path length, λ . (c) Between-group differences in small-world index, σ [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Correlations between node-based local gyrification and age of onset

	<i>r</i>	<i>p</i> (FDR-corrected)
lh gyrus rectus	0.328	<i>p</i> = .001
lh suborbital sulcus	0.355	<i>p</i> < .001
rh gyrus rectus	0.346	<i>p</i> < .001
rh subcallosal gyrus	0.318	<i>p</i> = .002
rh medial orbital sulcus	0.372	<i>p</i> < .001

Abbreviations: lh, left hemisphere; rh, right hemisphere; *r*, Pearson correlation coefficient; FDR, false discovery rate.

impaired task performance during a Tower of London Task assessing planning abilities. Furthermore, Kaller, Rahm, Spreer, Weiller, and Unterrainer (2011), similarly employing a Tower of London Task, found a dissociation between left and right DLPFC function with stronger activations in the left DLPFC correlating with higher demands on goal hierarchy in healthy subjects. This is interpreted as a stronger involvement of left DLPFC during goal extraction for a given problem. Hence, the decreased clustering coefficient of the left middle frontal sulcus indicating a reduced connectivity among its neighbors may constitute the structural basis of impaired planning abilities in OCD. However, it should be noted that a further study reported impairments in DLPFC activity related to impaired task performance not only for OCD but also other diagnostic categories including panic disorder and hypochondriasis (van den Heuvel et al., 2011). The authors therefore concluded that a common, disease-unspecific mechanism may underlie the impairments in planning ability. Thirdly, we report significant positive correlations between IGI's in several inferior frontal nodes and age of onset indicating that smaller IGI values are accompanied by earlier age of disease onset. The lack of group $\times$ age interactions may speak in favor of differences in gyrification networks indicating a potential early neurodevelopmental risk factor that appears to be independent of age related developmental trajectories. Additionally, the significant association with age of onset suggests that age of onsets itself seems to further influence these early alterations. However, due to the cross-sectional study design it is not possible to draw strong conclusions about these alterations to be best interpreted as trait markers. Nevertheless, the present findings might be used to generate hypotheses and spark further research into the subject-matter ideally applying longitudinal study designs. Additionally, it may be interesting to try to assess whether patients were born pre-term when studying structural brain alterations in general and gyrification in particular. Previous studies revealed a relationship between measures of integration and segregation with therapy outcomes in schizophrenia (Palaniyappan et al., 2016). Future work might therefore use gyrification-based network measures to examine relationships between gyrification and therapy outcome (responder, nonresponder) in OCD as well. Additionally, it would be of interest to conduct analyses based on sub-graphs that are binned into phases (e.g., early, mid, late) according to the developmental scheme of gyrification. Furthermore, comparing the relationship

between IGI values in OCD patients, their first-degree relatives, and healthy control subjects might shed more light on the importance of gyrification as a potential structural endophenotype.

5 | LIMITATIONS

Combining data from various centers using different acquisition protocols in order to substantially increase sample sizes may introduce systematic biases. This issue was addressed by adjusting IGI values for the scan sequence and thus coil type used. Nevertheless, some bias that cannot be removed using the applied statistical tools might remain and should be acknowledged. Due to the cross-sectional nature of the study design, it is not possible to draw strong conclusions regarding the idea of ascribing alterations in covariance patterns to time locked, sensitive periods. Additionally, very recent evidence by Cao et al. (2017) indicates that patients with various psychiatric disorders (major depression disorder, schizophrenia, and bipolar disorder I) display deviating gyrification trajectories over age when compared with healthy controls. However, the group $\times$ age interaction analyses revealed no such differences within the current sample implying a similar trajectory within OCD and healthy controls. This, in turn, speaks against a disease-related neurodegenerative or progressive process and supports our hypothesis of early neurodevelopmental alterations. Furthermore, the sample in the current study is age-matched and IGI values were adjusted for age-effects prior to computing correlation matrices. Another limiting factor lies within the rather heterogeneous sample regarding medication status as well as presence of comorbidities. To the best of our knowledge, there are no studies to date, that systematically examine the relationship between medication and gyrification. Additionally, previous work from our group (Rus et al., 2016) revealed that taking medication status as well as comorbidities into consideration did not significantly affect gyrification differences between OCD patients and healthy controls. Conducting exploratory sub group analyses of medicated/unmedicated patients as well as patients with and without comorbidity revealed no significant differences in the NBS results. However, a lack of significant differences does not necessarily imply a lack of relationship. Therefore, potential relationships should still be investigated in the future preferably using substantially larger sample sizes.

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