Disrupted Higher-Order Topology in OCD Brain Networks Revealed by Hodge Laplacian – an ENIGMA Study

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Introduction: Obsessive-compulsive disorder (OCD) is a disabling condition characterized by intrusive obsessions and repetitive compulsions that typically cause marked anxiety. Task and resting-state fMRI studies have implicated alterations in large-scale circuits in OCD, including the cortico–striatal–thalamic–cortical (CSTC) circuit and, more recently, sensorimotor pathways[1]. However, conventional fMRI analysis focus on pairwise functional connectivity (FC), which only represents the interactions between two nodes/brain regions, thus failing to capture the inherently higher-order, multi-nodal architecture of brain circuits. Topological data analysis (TDA) addresses this limitation by modeling data as simplicial complexes and tracking features across dimensions via persistent homology (PH)[2], where 1-simplices represent pairwise interactions, 2-simplices are triangles with 3-node interactions, and 3-simplices are tetrahedra with 4-node interactions, etc. PH alone, however, does not localize which specific topological structures differ between groups. Recently, Hodge Laplacian, a generalized graph Laplacian method, has been proposed to detect abnormal cycles and other higher-order structures in brain networks[3]. Here we applied the Hodge Laplacian based TDA framework to a large ENIGMA-OCD resting-state dataset to identify OCD-related alterations in 1-dimensional cycles that are not apparent in standard pairwise FC analysis.

Methods: Following the preprocessing pipeline described previously[4], we included 1024 participants with OCD and 1028 controls from 28 centers. In line with previous ENIGMA resting state analyses[4], timeseries were extracted based on 318 ROIs, comprising ROIs selected from the Schaefer-400, Harvard–Oxford, and Buckner-17 atlases, plus additional amygdala and accumbens coordinates from NeuroSynth. Subject level FC matrices were calculated using Pearson's correlation. Between group pairwise FC differences were

assessed using linear mixed effect (LME) models, including group as fixed effects, age, sex and head motion (framewise displacement, FD) as covariates, and site ID as a random intercept. To probe higher-order topology, we applied the Hodge Laplacian analysis for finding discriminating 1-dimensional cycles between OCD and controls. Brain networks were treated as 1-dimensional simplicial complexes, and the persistent homology-based graph filtration process was performed on the global averaged maximum spanning tree (MST). By adding one non-MST edge at a time, we were able to systematically enumerate all possible 1-cycles in the network. The Hodge Laplacian spectral decomposition was used to get algebraic representations of all 1-cycles, by computing the eigenvectors of zero eigenvalues of the Laplacian matrix. We estimated the subject-level cycle coefficients α by projecting the cycle vectors back onto individual FC networks using a least-squares approach. Site-stratified permutation tests were then performed on between-group differences in α. Age, sex, FD and sites effects were controlled using the Freedman-Lane procedure within the permutation framework[5]. Family-wise error rate (FWER) correction was implemented by comparing the T statistic of each cycle to the maximum T statistic observed across all cycles in each permutation. Finally, for the most discriminating cycles, we applied agglomerative clustering based on their functional network profiles.

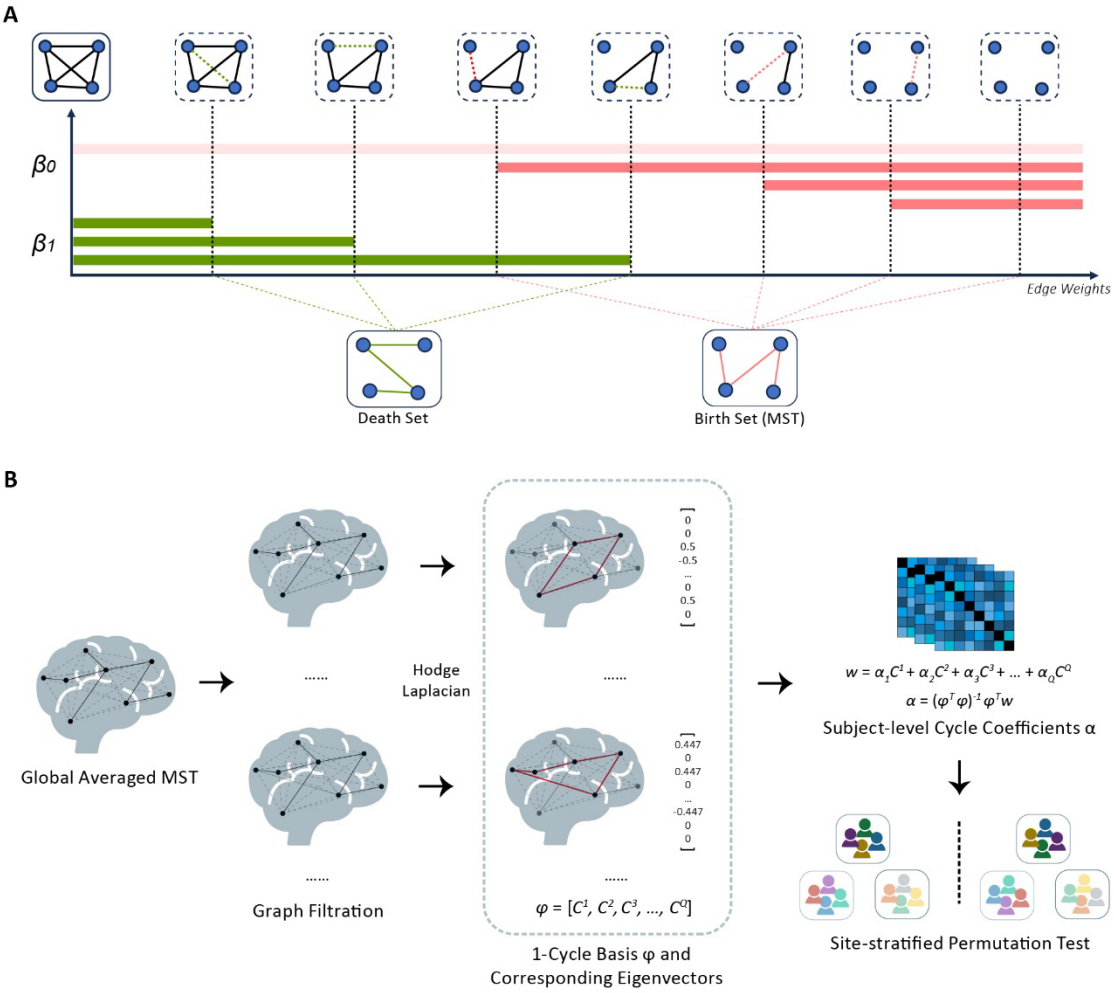

Fig 1. A Demonstration of graph filtration process. Based on the concept of persistent homology, we perform the graph filtration according to sorted edge weights. The number of connected components (β_0) and the number of cycles (β_1) change at different filtration values. Notice that a component has infinate death value and a cycle has infinate birth value, we can decompose edges into death set and birth set, and the birth set is exactly the maximum spanning tree (MST) structure of the graph. **B** Process of Hodge Laplacian on resting state brain networks.

Results: We identified 93 significant 1-cycles showing reduced strength in OCD compared to controls (FWER corrected p<0.05; Cohen's d = 0.223-0.283, partial R^2 = 0.012-0.019). Agglomerative clustering revealed 5 distinct functional profiles involving the Frontoparietal network (FPN, labeled "Control" in the atlas), Visual/Dorsal Attention network (Vis/DAN), Somatomotor network (SMN), Default Mode network (DMN), and SMN/Salience network (SN). Specifically, OCD patients exhibited weaker integration in these network-specific cycles which mostly spanned both hemispheres. Critically, these topological alterations were largely independent of pairwise connectivity differences. The majority of edges constituting these abnormal cycles did not exhibit significant group differences in standard FC analysis, indicating that Hodge-Laplacian-derived cycles capture higher-order, multi-nodal disruptions that are not detectable when assessing pairwise connectivity changes.

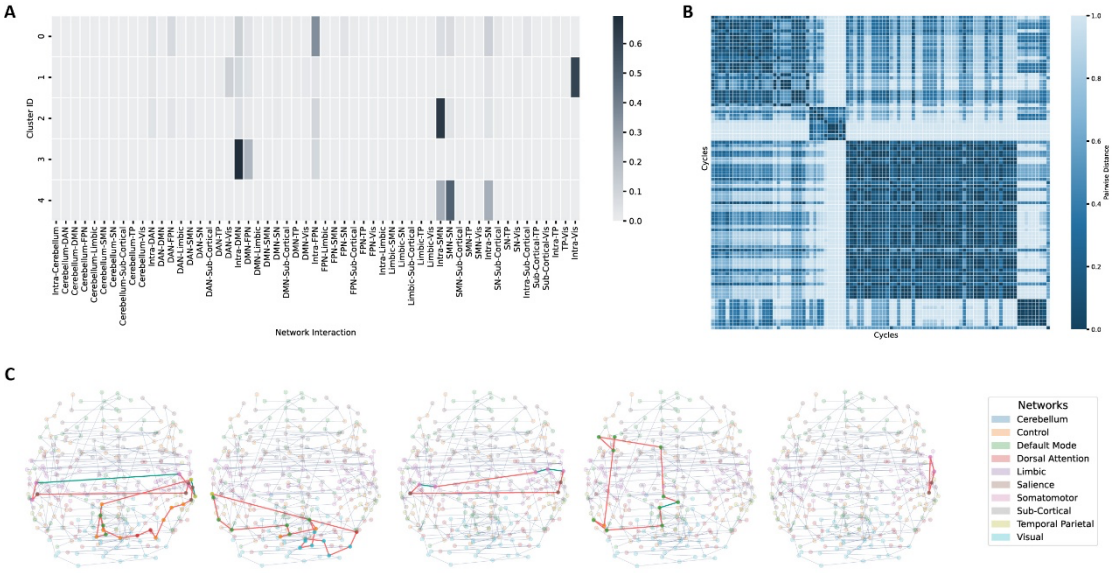

Fig 2. A Agglomerative clustering results according to functional profiles of cycles. **B** Pairwise cosine distances between cycles. 5 distinct clusters are showed in the heatmap. **C** Visualizations of the most discriminating 1-cycles in each cluster. Global averaged maximum spanning tree structure is showed in the background. Different colors of nodes indicate different brain networks. Highlighted edges demonstrate the higher-order cycle structure, with green color indicates the edge has significant functional connectivity strength difference between OCD and healthy controls. DAN: dorsal attention network, DMN: default mode network, FPN: frontal parietal network (labeled "Control" in the atlas), OCD: obsessive-compulsive disorder, SMN: somatomotor network, SN: salience network, TP: temporal parietal network, Vis: visual network.

Conclusions: This study provides the first large-scale evidence of abnormal higher-order topology in OCD using a Hodge Laplacian based TDA framework. By localizing abnormal 1-cycles in a multi-site resting-state mega-analysis, we identify distinct groups of altered cycles spanning FPN, Vis/DAN, SMN, DMN, and SMN/SN networks. These cycles concentrate in pathways linking core OCD domains: impaired cognitive control (FPN–DMN), excessive internal monitoring (DMN–SN), and compulsive motor behaviors (SMN–Vis/DAN). In comparison with the pairwise comparison results, we found these topological cycles to be composed of complex, multi-nodal interactions that were largely independent from the pairwise connectivities. The emergence of these disruptions only when modeling multi-nodal cycles suggests that OCD pathology reflects a breakdown in recurrent, higher-order circuit organization—specifically disrupted feedback loops that are undetectable via conventional pairwise analyses.

References:

1. Van Den Heuvel OA, Van Wingen G, Soriano-Mas C, et al. Brain circuitry of compulsivity. *Eur Neuropsychopharmacol*. 2016;26(5):810-827. doi:10.1016/j.euroneuro.2015.12.005

2. Phinyomark A, Ibanez-Marcelo E, Petri G. Resting-State fMRI Functional Connectivity: Big Data Preprocessing Pipelines and Topological Data Analysis. *IEEE Trans Big Data*. 2017;3(4):415-428. doi:10.1109/TBDATA.2017.2734883

3. Anand DV, Chung MK. Hodge Laplacian of Brain Networks. *IEEE Trans Med Imaging*. 2023;42(5):1563-1573. doi:10.1109/TMI.2022.3233876

4. Bruin WB, Abe Y, Alonso P, et al. The functional connectome in obsessive-compulsive disorder: resting-state mega-analysis and machine learning classification for the ENIGMA-OCD consortium. *Mol Psychiatry*. 2023;28(10):4307-4319. doi:10.1038/s41380-023-02077-0

5. Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. *NeuroImage*. 2014;92:381-397. doi:10.1016/j.neuroimage.2014.01.060