Proposal to ENIGMA-PGC

Redefining Resting-State Network Models of Posttraumatic Stress Disorder with Resolution Limit-Free Community Detection

Marisa Ross, MPA[1,2]
Josh Cisler, PhD[2]

1. Neuroscience and Public Policy Program, University of Wisconsin-Madison, Madison, WI
2. Department of Psychiatry, University of Wisconsin-Madison, Madison, WI

Marisa Ross, MPA
PhD Candidate
Neuroscience and Public Policy Program
Department of Psychiatry
University of Wisconsin-Madison
Madison, WI 53719
mross9@wisc.edu

A. Relevant Background

Interpersonal Violence (IPV) exposure, compared to other traumatic experiences such as motor vehicle accidents, greatly increases an individual's risk for developing posttraumatic stress disorder (PTSD) [1–3]. Relative to other anxiety disorders, PTSD carries a particularly high burden to the individual and society in the form of lowered quality of life and high comorbidity [3–5]. Even the gold-standard treatment for PTSD, Prolonged Exposure (PE) lacks efficacy, with remission rates of only ~40-60% for IPV victims[6,7]. As such, improvement of biomarkers for PTSD and treatment efficacy is paramount. Current neurocircuitry models of PTSD conceptualize the disorder as one of deficits in fear processing and emotion regulation, with ample evidence to suggest that PTSD is associated with increased acquisition of conditioned fear responses and resistance to extinguishing fears, [8–11] along with hypervigilance to threat cues[12,13]. These models generally focus on isolated nodes of the brain or functional connectivity between two nodes within a circuit. Indeed, the two most widely dominant neuroimaging analytic techniques include voxelwise functional activation analyses and voxelwise seed based-analyses during fMRI tasks that are designed to activate these regions. The former approach assumes each brain region (e.g., amygdala) acts as an isolated unit. The latter approach assumes there are only bivariate relationships between regions (e.g., amygdala-medial prefrontal cortex connectivity) that also operate in isolation from other bivariate relationships. As such, univariate and seed-based approaches carry considerable assumptions and limitations. An emerging literature posits that neural dysfunction in PTSD may be associated with dysfunction in large-scale functional networks rather than individual nodes or circuits[14–29]. This literature utilizes innovative analytical tools in neuroimaging to investigate neural network structure at rest[14,16–20,22,25,27,28] and during emotion[15,24]- and threat-processing[21] tasks to glean a better understanding of mechanisms for and consequences of network dysfunction in PTSD.

Functional Network Structure and Community Detection. Graph theory principles from the field of mathematics have proven particularly useful in neuroimaging for partitioning whole-brain signals into discrete networks and for characterizing properties of the nodes involved in the graph. The principles behind graph theory examine properties of networks and conceptualize these elements based on their intercorrelations[30]. While several large-scale brain networks have been identified and studied in the context of disease, three canonical networks appear to play a particularly important role in cognitive function and psychopathology, and therefore have been especially well defined. These networks, referred to as the central executive network (CEN), salience network (SN), and default mode network (DMN), are commonly found to be intrinsically coupled both in task and at rest[31,32] and are often cited as networks of altered connectivity in PTSD[18,20–25,27,28,33,34]. Briefly, the CEN is anchored in the dorsal lateral prefrontal cortex and posterior parietal cortex and plays a role in working memory, executive functioning and attention; the SN is anchored in the insular cortex and dACC and is important for detecting and mapping internally and externally salient events; and the DMN is important for self-referential mental activity and is anchored in the posterior cingulate and mPFC[32]. The CEN, SN, and DMN are generally conceptualized as three cohesive networks; thus, disruptions or fragmentation in their connectivity structure may underlie the uni- and bi-variate dysconnectivity observed in PTSD.

Several principles of graph theory are important for understanding brain network communication and dynamics that may be altered in psychopathology. The participation coefficient is a metric that reflects how well distributed a node's connections are throughout the graph, or the degree to which a node is connected to other nodes in separate modules [35,36]. The value of the participation coefficient will be close to one if the links are uniformly distributed amongst all modules and will approach zero if all of the connections are contained within the node's module [35]. A graph is considered highly modular if the average participation coefficient approaches zero, as this value indicates a segregated graph. Modular organization within biological systems has several theorized functions[36] that may become maladaptive in affective disorders such as PTSD. Researchers have demonstrated that modular organization promotes flexibility and adaptive response to varying environments through evolution and development [37–39] and it is theorized that modular systems are evolutionarily advantageous because systems with highly compartmentalized modules are less vulnerable to environmental perturbations than highly-interdependent systems [40–42]. Importantly for brain organization, modular networks have been demonstrated to promote and support functional specialization in information distribution and processing [43,44].

While several methods exist for determination of modular structure through community detection in graphs, few have been applied to PTSD samples and many have significant limitations. For brain functional network detection, the most pressing limitation is the resolution limit of modularity-maximizing functions. Briefly, when utilizing a modularity-maximizing function such as the popular Newman's Modularity[45–47], the investigator must choose a resolution parameter that defines the appropriate number of modules for the algorithm to

identify. This choice imposes an experimenter bias on an otherwise data-driven technique as well as a limit on the number of modules that can be detected, ultimately biasing results[45] and limiting the depth of hypotheses that can be tested; thus, development and validation of community detection algorithms that lack a resolution limit will be essential for determining true network alterations in affective psychopathology.

Altered Large-Scale Organization May Better Explain Traditional Univariate Neurocircuitry Deficits in PTSD. While the "optimal" degree of functional or structural network modularity is yet unknown, it follows that that alterations in modularity and fragmentation of network structure might result in maladaptive specialization of higher-order processing functions involved in emotional regulation and cognitive control in PTSD patients, deficits which are traditionally attributed to uni- and bi-variate dysconnectivity. For example, the altered connectivity of the fear-processing circuitry in PTSD (i.e. the amygdala, insular cortex, and dACC) is traditionally interpreted as bivariate hyperconnectivity of nodes within that circuit[48]; however, these nodes also form the SN and thus it is unclear at which level of organization the dysfunction lies. It is possible that the node-level hyperconnectivity observed in PTSD is better explained by a more integrated SN, resulting in increased connectivity of nodes within the SN in PTSD patients and forming a hyperspecialized network for salience detection. Similarly, the diminished ability of PTSD patients to extinguish fears, often attributed to hypoactivity of the hippocampus-vmPFC circuity, might be better explained by increased fragmentation or reduced within-network strength of the DMN and CEN such that communication between these essential nodes is disrupted. Examining dysfunction in fear circuitry from a network, rather than bivariate, level as proposed in this project may reveal complex dynamics that traditional models fail to detect, resulting in a fuller understanding of neural dysfunction in PTSD and the opportunity to examine network organization as a more reliable biomarker of psychopathology than univariate measures[49].

However, strong tests of hypotheses pertaining to network specialization in PTSD require robust and reliable community detection. Towards this goal, *this proposal will utilize a new method of community detection that does not suffer from drawbacks of resolution limits and relies on the quality function Asymptotical Surprise* [50,51]. This method will allow for testing of a more contemporary network model of PTSD that includes relative fragmentation and hyper-connectivity of large-scale functional networks. This method, through the use of a Partitioning Cost Optimization (PACO) algorithm[52], has recently been applied to resting-state fMRI data in healthy adults and schizophrenia patients in an attempt to circumvent the resolution limit of most community detection algorithms [53,54] and has proven to outperform other community detection methods[52], but has yet to be used in a PTSD sample or any other domain of affective psychopathology. PACO is a non-deterministic, agglomerative algorithm that maximizes partition quality by partitioning the graph based on proportions of internal and external edges from the connectivity matrix. Modularity is then determined by the probability of randomly drawing an internal edge from the distribution. PACO is also an entirely data-driven method because it does not require the selection of a resolution parameter and therefore can identify much smaller, more specific, functional modules based on unique connectivity patterns. PACO has the unique ability to illustrate relative fragmentation of canonical networks that are typically examined as whole, cohesive networks in psychopathology research and therefore can be used to identify underlying altered connectivity in PTSD. Thus, the potential for PACO in identifying specific, network-level dysfunction in PTSD is exciting and with clear theoretical implications.

B. Research Goal and Hypotheses

Goal: We propose to utilize the resting-state fMRI data of the ENIGMA-PGC PTSD consortium to characterize topological organization of functional network properties in adult women with IPV-related PTSD. To achieve this goal, we propose to use for the first time novel algorithms (e.g., PACO and Asymptotic Surprise) to define patterns of intrinsic network organization in a large PTSD sample and thereby define a contemporary and more neurophysiologically plausible understanding of the impact of PTSD on the organization of functional networks.

Hypotheses:

1. Relative to healthy controls, women with PTSD will demonstrate unique patterns of modular organization characterized by reduced global participation coefficient, increased modularity of the Salience Network, and decreased within-network strength of the Default Mode and Central Executive Networks.
2. Within the PTSD group, global participation coefficient, modularity of the Salience Network, and within-network strength of the Default Mode and Central Executive Networks will scale linearly with severity of IPV-exposure and psychiatric symptoms.

C. Analysis Plan and Preliminary Results

All resting-state fMRI scans will be preprocessed under the protocols from the ENIGMA consortium[55]. Following preprocessing, we will first define individual modular brain organization using a 500 regions-of-interest (ROI) atlas[56]. For each participant, we will calculate the mean time course of voxels within each ROI, excluding voxels within ROIs that were outside of the brain for a given individual, resulting in connectivity matrix for each participant. These matrices will be concatenated across participants, correlated, and r-to-z transformed, and all diagonals and negative values will be set to zero within the matrix. Each subject's connectivity matrix will then be thresholded to ensure a large, sparse graph with noisy connections removed and every node connected to at least one other node. Global modular brain organization for the group and each subject will be assessed through the use of the community detection quality function Asymptotical Surprise [50,51]. We will run the PACO algorithm 200,000 times to ensure identification of the optimal value of Asymptotical Surprise. This step will produce the number of functional modules for the group along with a spatial network map that will be applied to each individual. We will use the Brain Connectivity Toolbox within Matlab[57] to calculate network metrics, including participation coefficients and within-network strength for each individual. Each subject's global participation coefficient and within-network strength for each canonical network (SN, DMN, and CEN) will be carried forward to second-level analyses as the main variables of interest.

Finally, we will examine the relationships amongst modular brain organization (i.e. within-network strength of modules and global participation coefficient), group membership (PTSD or control) and individual difference variables including trauma severity score and PTSD symptom severity. We will use a linear regression model approach to examine relationships with these variables and network metrics, controlling for participant age and relevant clinical factors including comorbid psychiatric disorders. This step will allow for evaluation of the differences in large-scale network organization between groups in terms of the relative breakdown of regulatory functional connectivity in PTSD that is traditionally explained by uni- and bivariate models.

Preliminary Results. As a proof-of-concept, we used our existing resting-state dataset from 106 adult women with (n=85) and without (n=21) IPV-related PTSD to optimize atlas selection and the PACO algorithm. Due to the small size of our control dataset in relation to the PTSD dataset, we cannot draw any conclusions about differences between groups in network topology using this method. However, our preliminary results suggest that we can indeed utilize PACO and Asymptotical Surprise to resolve small communities within resting-state networks (Figure 1) and that these communities represent anatomically meaningful networks (Figure 2) that may relate to trauma exposure (Figure 3). The ENIGMA-PGC PTSD cohort would greatly assist in improving our sample size in both groups such that more robust conclusions can be made regarding altered network topology in a heterogeneous PTSD sample.

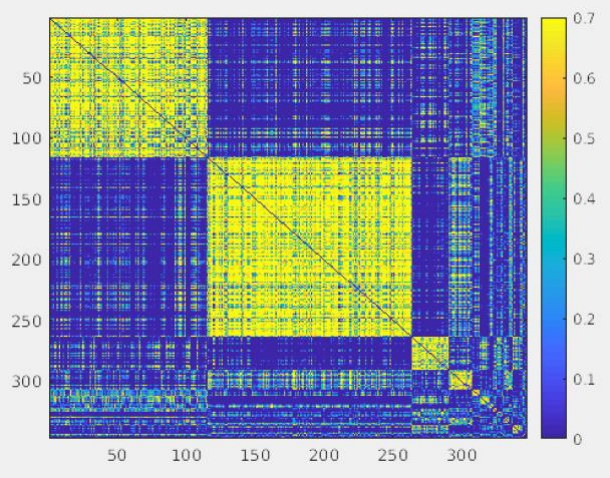

Figure 1: Group-level correlation matrix representing 20 unique communities resolved by PACO.

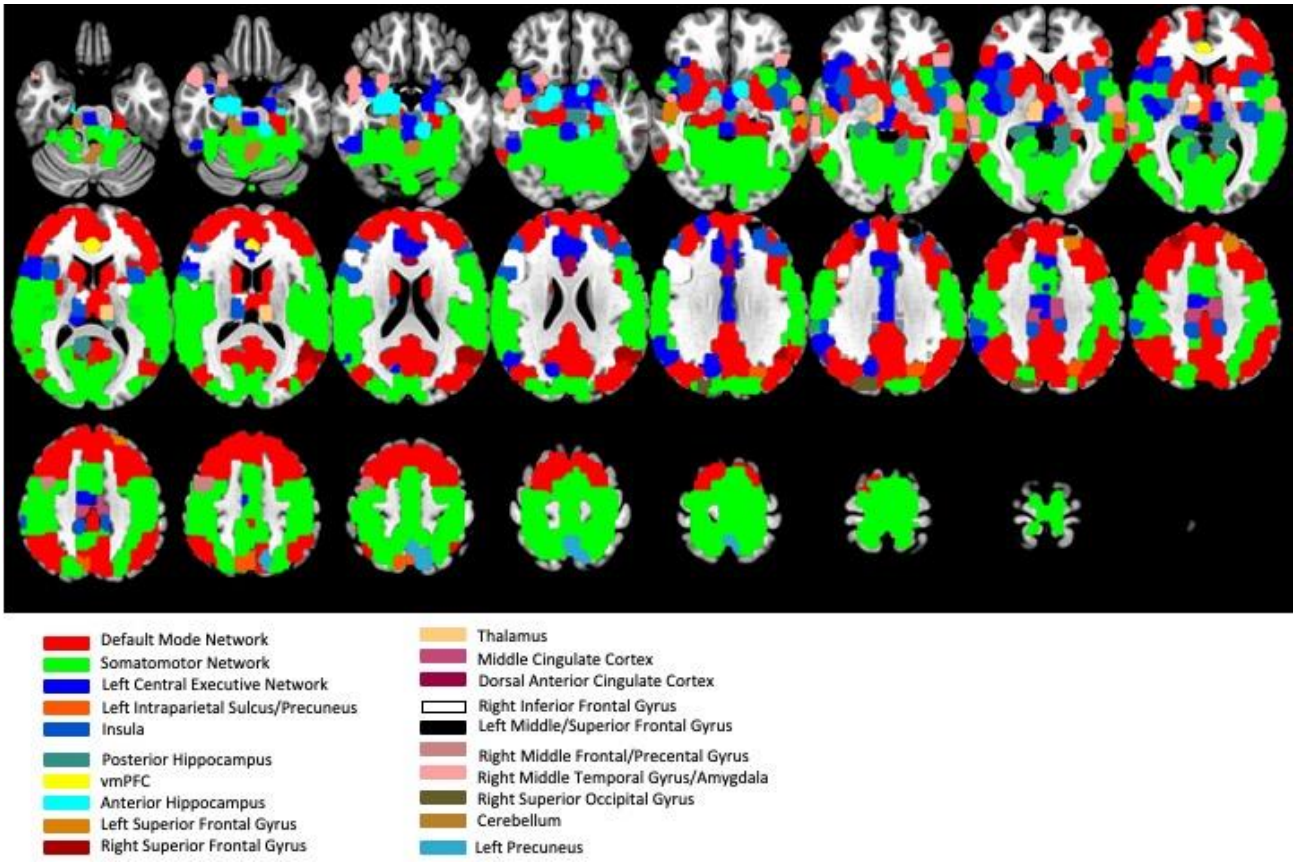

Figure 2: Group-level spatial map representing 20 unique communities defined by PACO.

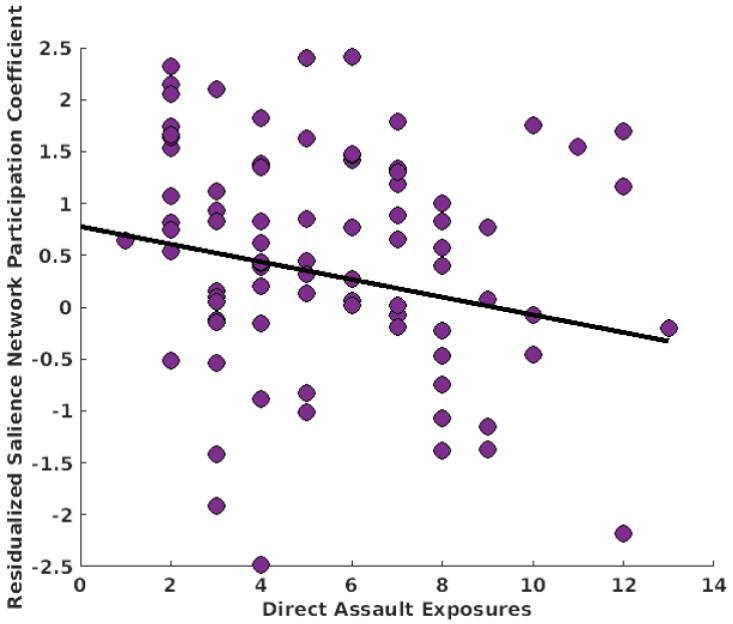

Figure 3: Participation coefficient of the Salience Network is inversely related to number of direct assault exposures in the PTSD group at a trend level ($t(80) = -1.89$, $p = .06$)

D. Analysis Personnel

1. Marisa Ross, MPA
2. Josh Cisler, PhD

E. Resources Needed

1. Preprocessed resting state fMRI timecourses from adult female subjects in the PGC-PTSD dataset
2. Clinical variables including PTSD symptom severity, types/amount of trauma exposure, childhood trauma, comorbid psychiatric diagnoses, and chronological age.
3. Relevant scanner and scan parameters for resting state fMRI dataset.

F. Timeline

We anticipate this project to take approximately 4 months to complete.

G. Collaboration

We agree to follow the standard PGC policy regarding secondary analyses. PGC investigators who are not named on this proposal but wish to substantively contribute to the analysis and manuscript are welcome to contact the proposing group to discuss joining the proposal.

H. Authorship

We will follow the authorship policy of the PGC-PTSD which can be found at https://pgc-ptsd.com/wp-content/uploads/2017/06/Authorship-Guidelines-PGC-PTSD.pdf

a) Are you following the authorship policies of the groups involved? ***YES***
b) Will there be a writing group and if so, who will be included? ***The writing group will be comprised of the investigative team listed above (Marisa Ross and Josh Cisler)***.
c) What groups or individuals will be listed as authors? ***Authors will include the writing group (M.R. and J.C.) plus individual and group contributors of data and analysis from each site (generally 2-3 co-authors from each site)***.
d) Will PGC members not listed as named authors be listed at the end of the manuscript? ***All individuals who meet the criteria established in the PGC-PTSD authorship policy will be co-authors. Other PGC members will not be listed at the end of the manuscript***.
e) Will PGC members or groups be listed as "collaborators" on the PubMed abstract page? ***All individuals and groups who meet the authorship criteria of the PGC-PTSD authorship policy will be listed as collaborators on the PubMed abstract page. No other individuals or groups will be listed***.
f) How will funding sources be handled or acknowledged? ***All funding sources that supported data collection and analysis will be listed in the manuscript***.

References

1 Kessler RC. Posttraumatic Stress Disorder: The Burden to the Individual and to Society. *J Clin Psychiatry* 2000;**61**:4–12.

2 Resnick HS, Kilpatrick DG, Dansky BS, Saunders BE, Best CL. Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women. *Journal of Consulting and Clinical Psychology* 1993;**61**:984.

3 Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 1995;**52**:1048–60.

4 Breslau N, Davis GC, Schultz LR. Posttraumatic Stress Disorder and the Incidence of Nicotine, Alcohol, and Other Drug Disorders in Persons Who Have Experienced Trauma. *Arch Gen Psychiatry* 2003;**60**:289–94. https://doi.org/10.1001/archpsyc.60.3.289.

5 Olatunji BO, Cisler JM, Tolin DF. Quality of life in the anxiety disorders: a meta-analytic review. *Clin Psychol Rev* 2007;**27**:572–81. https://doi.org/10.1016/j.cpr.2007.01.015.

6 Foa EB, Rothbaum BO, Riggs DS, Murdock TB. Treatment of posttraumatic stress disorder in rape victims: a comparison between cognitive behavioral procedures and counseling. *Journal of Consulting and Clinical Psychology* 1991;**59**:715–23. http://dx.doi.org.ezproxy.library.wisc.edu/10.1037//0022-006X.59.5.715.

7 Foa EB, Dancu CV, Hembree EA, Jaycox LH, Meadows EA, Street GP. A comparison of exposure therapy, stress inoculation training, and their combination for reducing posttraumatic stress disorder in female assault victims. *Journal of Consulting and Clinical Psychology* 1999;**67**:194–200. http://dx.doi.org.ezproxy.library.wisc.edu/10.1037/0022-006X.67.2.194.

8 Duits P, Cath DC, Lissek S, Hox JJ, Hamm AO, Engelhard IM, *et al.* Updated Meta-Analysis of Classical Fear Conditioning in the Anxiety Disorders. *Depress Anxiety* 2015;**32**:239–53. https://doi.org/10.1002/da.22353.

9 Peri T, Ben-Shakhar G, Orr SP, Shalev AY. Psychophysiologic assessment of aversive conditioning in posttraumatic stress disorder. *Biological Psychiatry* 2000;**47**:512–9.

10 Wessa M, Flor H. Failure of extinction of fear responses in posttraumatic stress disorder: evidence from second-order conditioning. *Am J Psychiatry* 2007;**164**:1684–92. https://doi.org/10.1176/appi.ajp.2007.07030525.

11 Norrholm SD, Jovanovic T, Olin IW, Sands LA, Karapanou I, Bradley B, *et al.* Fear extinction in traumatized civilians with posttraumatic stress disorder: relation to symptom severity. *Biol Psychiatry* 2011;**69**:556–63. https://doi.org/10.1016/j.biopsych.2010.09.013.

12 Pole N. The psychophysiology of posttraumatic stress disorder: a meta-analysis. *Psychol Bull* 2007;**133**:725–46. https://doi.org/10.1037/0033-2909.133.5.725.

13 Rauch SL, Whalen PJ, Shin LM, McInerney SC, Macklin ML, Lasko NB, *et al.* Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biological Psychiatry* 2000;**47**:769–76. https://doi.org/10.1016/S0006-3223(00)00828-3.

14 Cisler JM. Childhood Trauma and Functional Connectivity between Amygdala and Medial Prefrontal Cortex: A Dynamic Functional Connectivity and Large-Scale Network Perspective. *Front Syst Neurosci* 2017;**11**:29. https://doi.org/10.3389/fnsys.2017.00029.

15 Cisler JM, Privratsky A, Smitherman S, Herringa RJ, Kilts CD. Large-scale brain organization during facial emotion processing as a function of early life trauma among adolescent girls. *NeuroImage: Clinical* 2018;**17**:778–85. https://doi.org/10.1016/j.nicl.2017.12.001.

16 Ohashi K, Anderson CM, Bolger EA, Khan A, McGreenery CE, Teicher MH. Childhood maltreatment is associated with alteration in global network fiber-tract architecture independent of history of depression and anxiety. *Neuroimage* 2017;**150**:50–9. https://doi.org/10.1016/j.neuroimage.2017.02.037.

17 Puetz VB, Parker D, Kohn N, Dahmen B, Verma R, Konrad K. Altered brain network integrity after childhood maltreatment: A structural connectomic DTI-study. *Human Brain Mapping* 2017;**38**:855–68. https://doi.org/10.1002/hbm.23423.

18 Akiki TJ, Averill CL, Wrocklage KM, Scott JC, Averill LA, Schweinsburg B, *et al.* Default mode network abnormalities in posttraumatic stress disorder: A novel network-restricted topology approach. *Neuroimage* 2018;**176**:489–98. https://doi.org/10.1016/j.neuroimage.2018.05.005.

19 Xu J, Chen F, Lei D, Zhan W, Sun X, Suo X, *et al.* Disrupted Functional Network Topology in Children and Adolescents With Post-traumatic Stress Disorder. *Front Neurosci* 2018;**12**:. https://doi.org/10.3389/fnins.2018.00709.

20 Patriat R, Birn RM, Keding TJ, Herringa RJ. Default-Mode Network Abnormalities in Pediatric Posttraumatic Stress Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* 2016;**55**:319–27. https://doi.org/10.1016/j.jaac.2016.01.010.

21 Rabellino D, Tursich M, Frewen PA, Daniels JK, Densmore M, Théberge J, *et al.* Intrinsic Connectivity Networks in post-traumatic stress disorder during sub- and supraliminal processing of threat-related stimuli. *Acta Psychiatr Scand* 2015;**132**:365–78. https://doi.org/10.1111/acps.12418.

22 Reuveni I, Bonne O, Giesser R, Shragai T, Lazarovits G, Isserles M, *et al.* Anatomical and functional connectivity in the default mode network of post-traumatic stress disorder patients after civilian and military-related trauma. *Hum Brain Mapp* 2016;**37**:589–99. https://doi.org/10.1002/hbm.23051.

23 Shang J, Lui S, Meng Y, Zhu H, Qiu C, Gong Q, *et al.* Alterations in Low-Level Perceptual Networks Related to Clinical Severity in PTSD after an Earthquake: A Resting-State fMRI Study. *PLoS One* 2014;**9**:. https://doi.org/10.1371/journal.pone.0096834.

24 Thome J, Frewen P, Daniels JK, Densmore M, Lanius RA. Altered connectivity within the salience network during direct eye gaze in PTSD. *Borderline Personality Disorder and Emotion Dysregulation* 2014;**1**:17.
25 Zhang Y, Liu F, Chen H, Li M, Duan X, Xie B, *et al.* Intranetwork and internetwork functional connectivity alterations in post-traumatic stress disorder. *Journal of Affective Disorders* 2015;**187**:114–21. https://doi.org/10.1016/j.jad.2015.08.043.
26 Ross MC, Lenow JK, Kilts CD, Cisler JM. Altered neural encoding of prediction errors in assault-related posttraumatic stress disorder. *Journal of Psychiatric Research* 2018;**103**:83–90. https://doi.org/10.1016/j.jpsychires.2018.05.008.
27 Tursich M, Ros T, Frewen PA, Kluetsch RC, Calhoun VD, Lanius RA. Distinct intrinsic network connectivity patterns of post-traumatic stress disorder symptom clusters. *Acta Psychiatrica Scandinavica* 2015;**132**:29–38. https://doi.org/10.1111/acps.12387.
28 Ke J, Zhang L, Qi R, Xu Q, Zhong Y, Liu T, *et al.* Typhoon-Related Post-Traumatic Stress Disorder and Trauma Might Lead to Functional Integration Abnormalities in Intra- and Inter-Resting State Networks: a Resting-State Fmri Independent Component Analysis. *CPB* 2018;**48**:99–110. https://doi.org/10.1159/000491666.
29 Ross MC, Cisler JM. Altered large-scale functional brain organization in posttraumatic stress disorder: A comprehensive review of univariate and network-level neurocircuitry models of PTSD. *NeuroImage: Clinical* 2020;**27**:102319. https://doi.org/10.1016/j.nicl.2020.102319.
30 Bassett DS, Sporns O. Network neuroscience. *Nature Neuroscience* 2017;**20**:353–64. https://doi.org/10.1038/nn.4502.
31 Menon V. Developmental pathways to functional brain networks: emerging principles. *Trends in Cognitive Sciences* 2013;**17**:627–40. https://doi.org/10.1016/j.tics.2013.09.015.
32 Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in Cognitive Sciences* 2011;**15**:483–506. https://doi.org/10.1016/j.tics.2011.08.003.
33 Zhang X-D, Yin Y, Hu X-L, Duan L, Qi R, Xu Q, *et al.* Altered default mode network configuration in posttraumatic stress disorder after earthquake. *Medicine (Baltimore)* 2017;**96**:. https://doi.org/10.1097/MD.0000000000007826.
34 Roos A, Fouche J-P, Stein DJ. Brain network connectivity in women exposed to intimate partner violence: a graph theory analysis study. *Brain Imaging and Behavior* 2017;**11**:1629–39. https://doi.org/10.1007/s11682-016-9644-0.
35 Guimerà R, Nunes Amaral LA. Functional cartography of complex metabolic networks. *Nature* 2005;**433**:895–900. https://doi.org/10.1038/nature03288.
36 Sporns O, Betzel RF. Modular Brain Networks. *Annu Rev Psychol* 2016;**67**:613–40. https://doi.org/10.1146/annurev-psych-122414-033634.
37 Kashtan N, Alon U. Spontaneous evolution of modularity and network motifs. *PNAS* 2005;**102**:13773–8. https://doi.org/10.1073/pnas.0503610102.
38 Lipson H, Pollack JB, Suh NP. On the origin of modular variation. *Evolution* 2002;**56**:1549–56.
39 Sun J, Deem MW. Spontaneous Emergence of Modularity in a Model of Evolving Individuals. *Physical Review Letters* 2007;**99**:. https://doi.org/10.1103/PhysRevLett.99.228107.
40 Ellefsen KO, Mouret J-B, Clune J. Neural Modularity Helps Organisms Evolve to Learn New Skills without Forgetting Old Skills. *PLOS Computational Biology* 2015;**11**:e1004128. https://doi.org/10.1371/journal.pcbi.1004128.
41 Kirschner M, Gerhart J. Evolvability. *Proc Natl Acad Sci U S A* 1998;**95**:8420–7.
42 Wagner GP, Pavlicev M, Cheverud JM. The road to modularity. *Nature Reviews Genetics* 2007;**8**:921–31. https://doi.org/10.1038/nrg2267.
43 Espinosa-Soto C, Wagner A. Specialization Can Drive the Evolution of Modularity. *PLOS Computational Biology* 2010;**6**:e1000719. https://doi.org/10.1371/journal.pcbi.1000719.
44 Gallos LK, Makse HA, Sigman M. A small world of weak ties provides optimal global integration of self-similar modules in functional brain networks. *Proc Natl Acad Sci U S A* 2012;**109**:2825–30. https://doi.org/10.1073/pnas.1106612109.
45 Fortunato S, Barthelemy M. Resolution limit in community detection. *Proceedings of the National Academy of Sciences* 2007;**104**:36–41. https://doi.org/10.1073/pnas.0605965104.
46 Fortunato S. Community detection in graphs. *Physics Reports* 2010;**486**:75–174. https://doi.org/10.1016/j.physrep.2009.11.002.
47 Newman MEJ, Girvan M. Finding and evaluating community structure in networks. *Physical Review E* 2004;**69**:. https://doi.org/10.1103/PhysRevE.69.026113.
48 Admon R, Milad MR, Hendler T. A causal model of post-traumatic stress disorder: disentangling predisposed from acquired neural abnormalities. *Trends in Cognitive Sciences* 2013;**17**:337–47. https://doi.org/10.1016/j.tics.2013.05.005.
49 Nord CL, Gray A, Charpentier CJ, Robinson OJ, Roiser JP. Unreliability of putative fMRI biomarkers during emotional face processing. *Neuroimage* 2017;**156**:119–27. https://doi.org/10.1016/j.neuroimage.2017.05.024.
50 Traag VA, Aldecoa R, Delvenne J-C. Detecting communities using asymptotical surprise. *Phys Rev E* 2015;**92**:022816. https://doi.org/10.1103/PhysRevE.92.022816.
51 Xiang J, Zhang Y, Li J-M, Li H-J, Li M. Identifying multi-scale communities in networks by asymptotic surprise n.d.:18.
52 Nicolini C, Bordier C, Bifone A. Community detection in weighted brain connectivity networks beyond the resolution limit. *NeuroImage* 2017;**146**:28–39. https://doi.org/10.1016/j.neuroimage.2016.11.026.
53 Bordier C, Nicolini C, Forcellini G, Bifone A. Disrupted modular organization of primary sensory brain areas in schizophrenia. *Neuroimage Clin* 2018;**18**:682–93. https://doi.org/10.1016/j.nicl.2018.02.035.

54 Nicolini C, Bifone A. Modular structure of brain functional networks: breaking the resolution limit by Surprise. *Scientific Reports* 2016;**6**:19250. https://doi.org/10.1038/srep19250.
55 Adhikari BM, Jahanshad N, Shukla D, Turner J, Grotegerd D, Dannlowski U, *et al.* A resting state fMRI analysis pipeline for pooling inference across diverse cohorts: an ENIGMA rs-fMRI protocol. *Brain Imaging Behav* 2019;**13**:1453–67. https://doi.org/10.1007/s11682-018-9941-x.
56 Craddock RC, James GA, Holtzheimer PE, Hu XP, Mayberg HS. A whole brain fMRI atlas generated via spatially constrained spectral clustering. *Hum Brain Mapp* 2012;**33**:1914–28. https://doi.org/10.1002/hbm.21333.
57 Rubinov M, Sporns O. Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage* 2010;**52**:1059–69. https://doi.org/10.1016/j.neuroimage.2009.10.003.