Using tolerance intervals to capture heterogeneity in neuro-biological abnormalities within PTSD patients

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Background: A major challenge in studying post-traumatic stress disorder (PTSD) is its clinical heterogeneity [1][2], which is likely underlined by various neuro-biological abnormalities. This heterogeneity limits the ability to study the neurophysiological basis of the disorder using standard group-comparison approaches. To date, most efforts to characterize PTSD subtypes and develop diagnostic biomarkers involved identifying clusters of symptoms that tend to co-occur and testing for corresponding neurophysiological patterns (e.g. [3][4]). However, a specific clinical phenotype may be driven by several different neurophysiological factors. Moreover, a specific neurophysiological abnormality may have different clinical expressions in different people, due to other factors. An alternative to subtyping patients based on co-occurring clinical symptoms is to seek shared signatures of brain dysfunction/abnormality within patients that will uncover neurophysiological subtypes [5][6]. Such an approach has already provided some insight into how different neurophysiological patterns may lead to heterogeneity within clinical phenotype in psychotic disorders [7][5][8][9][10][6]. Neuroimaging-based biomarkers of abnormal brain function have been identified for several neuropsychiatric disorders [6][11] and have shown promise in predicting treatment response [12][13][14][6][15] and informing treatment selection[16].

Resting state fMRI is a useful modality for studying brain function in patient population, as it does not require any complicated task performance. The functional connectivity (FC) profiles estimated from this data within and between known functional brain networks are closely related to structural and synaptic measures of connectivity [17][18][19][20]. And group-level analysis of rsfMR data recorded from PTSD patients have shown abnormalities in FC within the DMN and VAN and between the DMN and both the VAN and FPCN [21][22][23], some of which were associated with specific behavioral measures. . These studies suggest that FC measures extracted from resting state fMRI can be used to identify novel neurobiological subtypes within PTSD patient population, with the potential for informing diagnosis and treatment. However, the challenge of extracting the relevant features that would best parse the heterogeneity within patients remains.

In this study we propose to adopt a normative modeling/conformal prediction approach for examining neurobiological heterogeneity within PTSD patients. We plan to do this by using statistical tolerance intervals (TIs) calculated on the control population to extract informative features from rsfMRI data and detect patterns of abnormality in patients. A tolerance interval is an interval that cover a certain proportion of the population with a certain degree of confidence and is often used for mapping individual abnormalities with respect to a reference population. We plan to use TIs calculated on healthy controls to model the distribution of normal FC within healthy controls, and identify abnormality-enriched FC features, that will allow to capture distinct neural signatures characterizing subpopulations within patients.

Analysis plan: resting state fMRI connectivity feature will be extracted from the data using a pre-defined functional parcellation [24]. We plan to further reduce data dimensionality by averaging the pairwise functional connectivity (FC) will be calculated using Pearson correlation and averaged for each region to obtain a measure of FC to each of 7 previously-defined resting networks [25].

We will explore the use of TIs for feature selection by incorporating them into a 10 fold cross-validation procedure for training a model to distinguish between PTSD patients and trauma exposed healthy controls. Within each cross-validation iteration, we plan to select features using TIs that will be calculated for each feature within healthy control population. Informative features will then be selected based on increased abnormality within patients, and used to train a model. We will also explore the contribution of combining a clustering analysis within each such iteration, as it has been shown to allow improved classification accuracy [6]. To this end we plan to make use the CLICK clustering algorithm [26] that automatically identifies the optimal number of clusters. For model training we plan to start with a linear-kernel support vector machine and may try additional classification methods as well. As a reference point to the above we will also conduct a parallel analysis that will make use of a standard t-test for feature selection.

After estimating the predictive power of rsfMRI FC features selected with TIs we plan to use the features that are consistently selected in the 10 FCV procedure for to identify subtypes within patient population, which will be further characterized according to behavioral and clinical data.

Our preliminary analysis was conducted on resting state fMRI data that was recorded from 93 unmedicated PTSD patients and 146 healthy combat veterans. Initial findings suggest that the use of TIs tends to select a unique set of feature most of which are not selected using a standard ttest approach, and leads to similar classification accuracy (TIs: accuracy=71; ttest: accuracy=71%) with a higher specificity (TIs: 82%; ttest: 77%) and a lower sensitivity (TIs: 60%; ttest:65%). Consistently selected features were shown to produce two clusters within patients. These clusters differed in subjective measure of affective state and emotion regulation (PANAS positive and ERQ_CR).

References:

[1] D. J. Stein, K. A. McLaughlin, K. C. Koenen, L. Atwoli, M. J. Friedman, E. D. Hill, A. Maercker, M. Petukhova, V. Shahly, and M. Ommeren, “DSM-5 and ICD-11 definitions of posttraumatic stress disorder: Investigating ‘narrow’ and ‘broad’ approaches,” *Depress. Anxiety*, vol. 31, no. 6, pp. 494–505, 2014.

[2] F. Edition, *Diagnostic and statistical manual of mental disorders*. Am Psychiatric Assoc, 2013.

[3] R. Daniela, D. Maria, H. Sherain, J. Théberge, M. M. C., and L. R. A., “Resting-state functional connectivity of the bed nucleus of the stria terminalis in post-traumatic stress disorder and its dissociative subtype,” *Hum. Brain Mapp.*, vol. 39, no. 3, pp. 1367–1379, Dec. 2017.

[4] S. Harricharan, A. A. Nicholson, M. Densmore, J. Théberge, M. C. McKinnon, R. W. J. Neufeld, and R. A. Lanius, “Sensory overload and imbalance: Resting-state vestibular connectivity in PTSD and its dissociative subtype,” *Neuropsychologia*, vol. 106, pp. 169–178, 2017.

[5] B. A. Clementz, J. Sweeney, J. Hamm, E. I. Ivleva, L. Ethridge, G. Pearlson, M. Keshavan, and C. A. Tamminga, *Identification of Distinct Psychosis Biotypes Using Brain-Based Biomarkers*, vol. 173. 2015.

[6] A. T. Drysdale, L. Grosenick, J. Downar, K. Dunlop, Y. Meng, R. Fetcho, B. Zebley, D. J. Oathes, A. F. Schatzberg, K. Sudheimer, J. Keller, H. S. Mayberg, M. Faith, G. S. Alexopoulos, M. D. Fox, A. Pascual-leone, U. Henning, B. J. Casey, M. J. Dubin, and C. Liston, "Resting State Connectivity Biomarkers Define Neurophysiological Biotypes of Depression," pp. 1–3.

[7] A. F. Marquand, T. Wolfers, M. Mennes, J. Buitelaar, and C. F. Beckmann, "Beyond Lumping and Splitting: A Review of Computational Approaches for Stratifying Psychiatric Disorders," *Biol. Psychiatry Cogn. Neurosci. Neuroimaging*, vol. 1, no. 5, pp. 433–447, 2016.

[8] A. Anticevic, M. S. Brumbaugh, A. M. Winkler, L. E. Lombardo, J. Barrett, P. R. Corlett, H. Kober, J. Gruber, G. Repovs, M. W. Cole, J. H. Krystal, G. D. Pearlson, and D. C. Glahn, "Global Prefrontal and Fronto-Amygdala Dysconnectivity in Bipolar I Disorder with Psychosis History," *Biol. Psychiatry*, vol. 73, no. 6, pp. 565–573, Mar. 2013.

[9] A. Anticevic, M. W. Cole, J. D. Murray, P. R. Corlett, X.-J. Wang, and J. H. Krystal, "The Role of Default Network Deactivation in Cognition and Disease," *Trends Cogn. Sci.*, vol. 16, no. 12, pp. 584–592, Dec. 2012.

[10] S. K. Hill, J. L. Reilly, R. S. E. Keefe, J. M. Gold, J. R. Bishop, E. S. Gershon, C. A. Tamminga, G. D. Pearlson, M. S. Keshavan, and J. A. Sweeney, "Neuropsychological Impairments in Schizophrenia and Psychotic Bipolar Disorder: Findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Study," *Am. J. Psychiatry*, vol. 170, no. 11, pp. 1275–1284, Nov. 2013.

[11] T. Yamada, R. I. Hashimoto, N. Yahata, N. Ichikawa, Y. Yoshihara, Y. Okamoto, N. Kato, H. Takahashi, and M. Kawato, "Resting-state functional connectivity-based biomarkers and functional mri-based neurofeedback for psychiatric disorders: A challenge for developing theranostic biomarkers," *Int. J. Neuropsychopharmacol.*, vol. 20, no. 10, pp. 769–781, 2017.

[12] C. Liston, A. C. Chen, B. D. Zebley, A. T. Drysdale, R. Gordon, B. Leuchter, H. U. Voss, B. J. Casey, A. Etkin, and M. J. Dubin, "Default mode network mechanisms of transcranial magnetic stimulation in depression," *Biol. Psychiatry*, vol. 76, no. 7, pp. 517–526, 2014.

[13] T. V Salomons, K. Dunlop, S. H. Kennedy, A. Flint, J. Geraci, P. Giacobbe, and J. Downar, "Resting-state cortico-thalamic-striatal connectivity predicts response to dorsomedial prefrontal rTMS in major depressive disorder," *Neuropsychopharmacology*, vol. 39, no. 2, p. 488, 2014.

[14] M. L. Phillips, H. W. Chase, Y. I. Sheline, A. Etkin, J. R. C. Almeida, T. Deckersbach, and M. H. Trivedi, "Identifying predictors, moderators, and mediators of antidepressant response in major depressive disorder: neuroimaging approaches," *Am. J. Psychiatry*, vol. 172, no. 2, pp. 124–138, 2015.

[15] G. Salvadore, B. R. Cornwell, F. Sambataro, D. Latov, V. Colon-Rosario, F. Carver, T. Holroyd, N. DiazGranados, R. Machado-Vieira, and C. Grillon, "Anterior cingulate desynchronization and functional connectivity with the amygdala during a working memory task predict rapid antidepressant response to ketamine," *Neuropsychopharmacology*, vol. 35, no. 7, p. 1415, 2010.

[16] C. L. McGrath, M. E. Kelley, P. E. Holtzheimer, B. W. Dunlop, W. E. Craighead, A. R. Franco, R. C.

Craddock, and H. S. Mayberg, “Toward a neuroimaging treatment selection biomarker for major depressive disorder,” *JAMA psychiatry*, vol. 70, no. 8, pp. 821–829, 2013.

[17] S. M. Smith, D. Vidaurre, C. F. Beckmann, M. F. Glasser, M. Jenkinson, K. L. Miller, T. E. Nichols, E. C. Robinson, G. Salimi-Khorshidi, and M. W. Woolrich, “Functional connectomics from resting-state fMRI,” *Trends Cogn. Sci.*, vol. 17, no. 12, pp. 666–682, 2013.

[18] D. C. Van Essen and K. Ugurbil, “The future of the human connectome,” *Neuroimage*, vol. 62, no. 2, pp. 1299–1310, 2012.

[19] M. D. Fox, A. Z. Snyder, J. L. Vincent, M. Corbetta, D. C. Van Essen, and M. E. Raichle, “The human brain is intrinsically organized into dynamic, anticorrelated functional networks,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 102, no. 27, pp. 9673–9678, 2005.

[20] M. E. Raichle, A. M. MacLeod, A. Z. Snyder, W. J. Powers, D. A. Gusnard, and G. L. Shulman, “A default mode of brain function,” *Proc. Natl. Acad. Sci.*, vol. 98, no. 2, pp. 676–682, 2001.

[21] J. K. Daniels, A. C. McFarlane, R. L. Bluhm, K. A. Moores, C. R. Clark, M. E. Shaw, P. C. Williamson, M. Densmore, and R. A. Lanius, “Switching between executive and default mode networks in posttraumatic stress disorder: alterations in functional connectivity.,” *J. Psychiatry Neurosci.*, 2010.

[22] Y. Zhang, F. Liu, H. Chen, M. Li, X. Duan, B. Xie, and H. Chen, “Intranetwork and internetwork functional connectivity alterations in post-traumatic stress disorder,” *J. Affect. Disord.*, vol. 187, pp. 114–121, 2015.

[23] S. B. J. Koch, M. Zuiden, L. Nawijn, J. L. Frijling, D. J. Veltman, and M. Olff, “Aberrant resting-state brain activity in posttraumatic stress disorder: A meta-analysis and systematic review,” *Depress. Anxiety*, vol. 33, no. 7, pp. 592–605, 2016.

[24] A. Schaefer, R. Kong, E. M. Gordon, T. O. Laumann, X.-N. Zuo, A. J. Holmes, S. B. Eickhoff, and B. T. T. Yeo, “Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI,” *Cereb. Cortex*, pp. 1–20, 2017.

[25] B. T. Thomas Yeo, F. M. Krienen, J. Sepulcre, M. R. Sabuncu, D. Lashkari, M. Hollinshead, J. L. Roffman, J. W. Smoller, L. Zöllei, and J. R. Polimeni, “The organization of the human cerebral cortex estimated by intrinsic functional connectivity,” *J. Neurophysiol.*, vol. 106, no. 3, pp. 1125–1165, 2011.

[26] R. Sharan, A. Maron-Katz, and R. Shamir, “CLICK and EXPANDER: A system for clustering and visualizing gene expression data,” *Bioinformatics*, vol. 19, no. 14, 2003.