Quantifying connectivity-derived Circuit Scores related to the Negative Valence Domain in Anxiety and Depression

Leonardo Tozzi[1], Elena Tuzhilina[2], Brooke Staveland[1], Bailey Holt-Gosselin[1], Sarah Chang[1], Melissa Shiner[1], David Choi[1], Trevor Hastie[3], Leanne Williams[1,3]
with the HCP-DES Investigator Team*

1. Department of Psychiatry and Behavioral Sciences, Stanford University, 401 Quarry Road, Stanford, CA 94305;
2. Department of Statistics, Stanford University, 390 Serra Mall, Stanford, CA 94305
3.Veterans Affairs Palo Alto Health Care System, 3801 Miranda Ave, Palo Alto, CA 94304

Background

Depression and anxiety affect over 400 million people globally and are leading causes of disability.[1] At present, diagnostic criteria don't take into account their neural underpinnings. To provide a new framework for the investigation of mental disorders, the NIH has launched the Research Domain Criteria (RDoC) initiative, which is centered around psychological constructs reflecting contemporary knowledge about major neural systems.

The Human Connectome Project for disordered emotional states (HCP-DES) aims to map anatomical and functional connectivity in anxiety and depression. It relies on RDoC and includes a battery of questionnaires matched by domain with fMRI tasks. Here, we use a large sample of healthy participants from the HCP Healthy Young Adult (HYA) release to assess the correspondence between questionnaires and an fMRI task assessing the negative valence domain. We use this information to compute a circuit score which is the linear combination of functional connections maximally associated with internal emotional states. Finally, in the HCP-DES dataset, we compare circuit scores between controls and anxious as well as depressed participants.

Participants

We downloaded the data of 875 participants (age: 28.69 ± 3.75, F = 401) from the HCP-HYA data release who showed no quality issues and had completed at least 50% of the Emotion fMRI task. As a self-reported measure, we used the Emotion Battery of questionnaires from the NIH toolbox.

HCP-HYA NIH Emotion Battery Scores (mean ± S.D.)

Negative Affect		**Stress & Self-Efficacy**		**Social Relationships**	
Anger (affect)	47.67 ± 8.15	Perceived stress	48.04 ± 9.17	Friendship	50.41 ± 9.02
Anger (hostility)	50.30 ± 8.62	Self efficacy	50.99 ± 8.30	Loneliness	51.03 ± 8.60
Anger (aggression)	51.72 ± 8.94	**Psychological Well-Being**		Perceived hostility	48.55 ± 8.55
Fear (affect)	50.11 ± 7.90	Life satisfaction	54.69 ± 9.23	Perceived rejection	48.32 ± 8.80
Fear (somatic)	51.74 ± 8.18	Purpose	51.99 ± 8.75	Emotional support	51.62 ± 9.65
Sadness	46.19 ± 7.81	Positive affect	50.11 ± 7.83	Instrumental support	48.11 ± 8.94

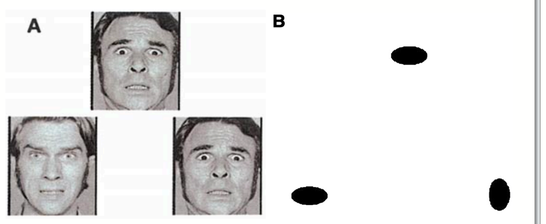
Participants from HCP-DES were 49 healthy controls (age: 35.84 ± 13.51, F = 26) and 28 participants with anxious and depressive symptoms (age: 25.97 ± 4.42, F = 19).

Hypothesis

Circuit scores based on functional connections related to subjective measures of affective state are altered in depression and anxiety

fMRI Methods

Emotion Task



In the fMRI task, participants matched angry/fearful faces (A) or shapes (B) on the bottom of the screen with one at the top. Six trials for 3 blocks were presented for each stimulus (duration=2s, ITI=1s).

Acquisition

HCP-HYA: 32 channel head coil on a modified 3T Siemens Skyra with TR = 720 ms, TE = 33.1 ms, flip angle = 52 deg, in-plane FOV = 208 × 180 mm, 72 slices, 2.0 mm isotropic voxels, multi-band factor 8. Two runs, right-left and left-right phase encoding.

HCP-DES: 32 channel head coil on GE Discovery with TR = 710 ms, TE = 30 ms, flip angle = 54 deg, in-plane FOV = 220.8 × 220.8 mm, 60 slices, 2.4 mm isotropic voxels, multi-band factor 6. One run, posterior-anterior phase encoding.

Preprocessing and subject-level analyses

Preprocessing was conducted with the Minimal Processing Pipeline developed by the HCP (cortical segmentation, fieldmap correction, warping to grayordinate space).[2] Then, physiological noise and motion were regressed from the data using aCompCor[3] and the Friston 24[4] motion parameters. Mean timeseries were extracted from areas defined by the Glasser multimodal parcellation[5] (cortical) and Freesurfer parcellation (subcortical). Connectivity matrices were built by correlating the resulting timeseries.

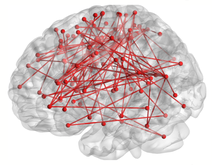
Derivation of circuit scores

HCP-HYA data

Questionnaires

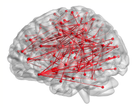
17 scales x 875 subjects

Task connectivity



379 x 379 regions x 875 subjects

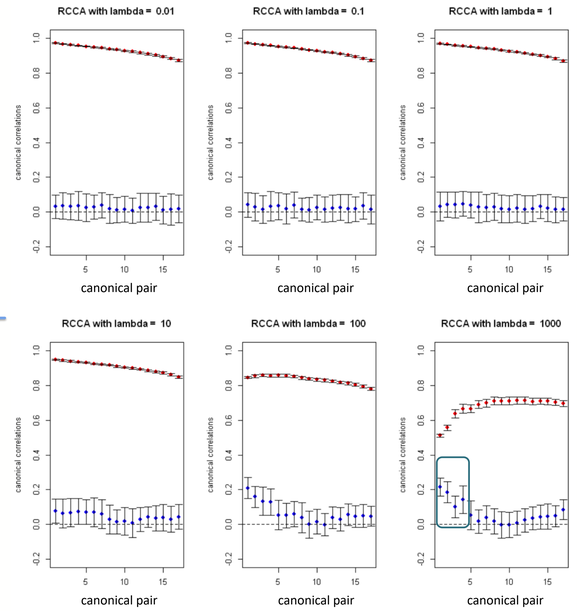
PCA (90% var. explained)



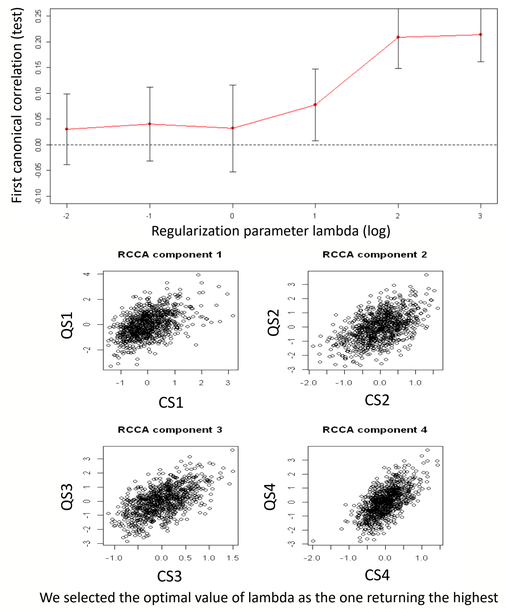
512 PCs x 875 subjects

RCCA finds weights (loadings) so that the linear combination of questionnaires and connectivity is maximally correlated.

Regularized cross-validated canonical correlation (RCCA)



RCCA correlations were higher for training (red) compared to test (blue) data, indicating overfitting for low values of the regularization parameter lambda.

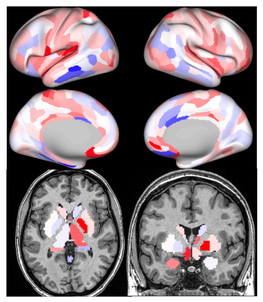


We selected the optimal value of lambda as the one returning the highest average correlation between questionnaires and connectivity in the test data for the first canonical pair across folds. This returned 4 circuit scores (CS) which had an average correlation >0 with corresponding questionnaires scores (QS).

Circuit score loadings

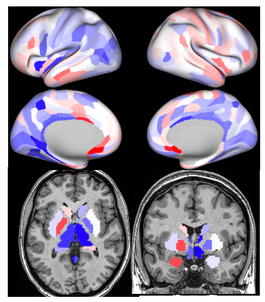
Circuit score 1

Scale	B
Purpose	-0.061
Emotional support	-0.028
Instrumental support	-0.013
Perceived stress	-0.012
Anger (hostility)	-0.012
Perceived rejection	-0.005
Positive affect	0.003
Loneliness	0.010
Fear (somatic)	0.021
Fear (affect)	0.021
Sadness	0.023
Anger (affect)	0.024
Perceived hostility	0.030
Friendship	0.034
Anger (aggression)	0.038
Life satisfaction	0.040
Self efficacy	0.076



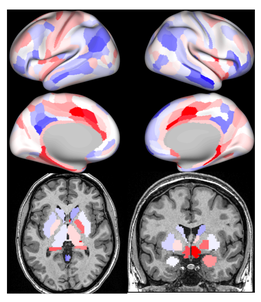
Circuit score 2

Scale	B
Fear (affect)	-0.081
Emotional support	-0.066
Loneliness	-0.050
Friendship	-0.048
Life satisfaction	-0.043
Perceived rejection	-0.007
Perceived hostility	-0.007
Anger (affect)	0.002
Perceived stress	0.005
Anger (hostility)	0.005
Sadness	0.013
Self efficacy	0.015
Fear (somatic)	0.027
Instrumental support	0.030
Purpose	0.035
Positive affect	0.036
Anger (aggression)	0.039



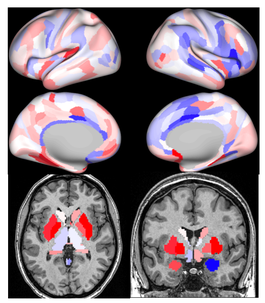
Circuit score 3

Scale	B
Emotional support	-0.066
Fear (somatic)	-0.046
Life satisfaction	-0.040
Anger (affect)	-0.033
Self efficacy	-0.029
Loneliness	-0.018
Instrumental support	-0.011
Perceived stress	-0.011
Perceived hostility	-0.011
Positive affect	-0.005
Anger (aggression)	<0.001
Anger (hostility)	0.014
Fear (affect)	0.028
Purpose	0.040
Perceived rejection	0.043
Sadness	0.048
Friendship	0.062



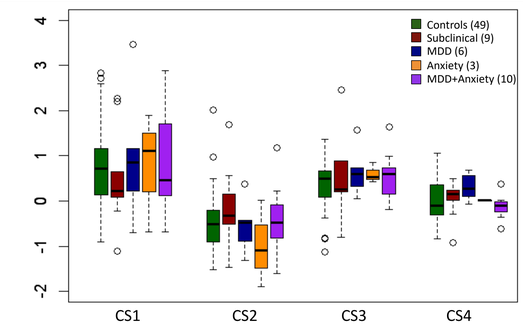
Circuit score 4

Scale	B
Life satisfaction	-0.065
Anger (affect)	-0.062
Anger (aggression)	-0.062
Sadness	-0.027
Perceived rejection	-0.015
Instrumental support	-0.006
Fear (affect)	0.005
Purpose	0.012
Friendship	0.023
Perceived hostility	0.025
Loneliness	0.028
Fear (somatic)	0.031
Anger (hostility)	0.040
Emotional support	0.043
Self efficacy	0.050
Positive affect	0.053
Perceived stress	0.071



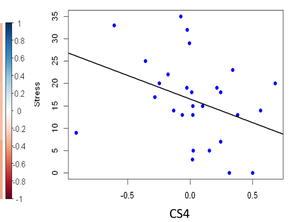
Tables show the loadings of the questionnaire scales for each of the four canonical pairs.
Figures show the average loading of all functional connections from each brain region to all others for each of the four canonical pairs (accounting for the PCA loadings).

Group comparison



In the HCP-DES dataset, we compared CS in controls and in a preliminary sample of patients grouped by DSM diagnosis. Some participants endorsing anxiety and depression did not qualify for a DSM diagnosis ("subclinical"). We found no differences between the groups. CS=circuit score, MDD=major depressive disorder.

	CS1	CS2	CS3	CS4
Depression	r=0.22 p=0.26	r=-0.06 p=0.76	r=0.02 p=0.91	r=-0.32 p=0.10
Anxiety	r=0.22 p=0.22	r=-0.08 p=0.69	r=0.18 p=0.36	r=-0.30 p=0.12
Stress	r=0.13 p=0.51	r=-0.11 p=0.58	r=0.10 p=0.61	r=-0.38 p=0.04



We calculated Spearman correlations between CS and scores from the Depression Anxiety Stress scale (DASS) in clinical participants. We found a correlation between stress and CS4. CS=circuit score.

References & Acknowledgements

1. Whiteford, H. A. et al. 2010. The Lancet, 382(9904), 1575-1586.
2. Glasser, M. F. et al. 2013. Neuroimage, 80, 105-124.
3. Bezhadi, Y. et al. 2007, Neuroimage, 37, 90-101.
4. Friston, K. et al. 1997, Neuroimage, 6, 218-219.
5. Glasser, M. F. et al. 2016, Nature, 536, 171-178.
6. Fusar-Poli, P. et al. 2009. J Psychiatry Neurosci., 34, 418–432.

Funding is provided by the National Institutes of Health (grant # U01MH109985 under PAR-14-281).
* We acknowledge our Co-Investigators Drs. Ian Gotlib, Brian Wandell, Max Wintermark, Adam Kerr and Russel Poldrack.

Conclusion

In the present work, we show that functional connectivity during an emotion processing task contains information related to subjective reports of emotional experiences in everyday life. The correlations returned by RCCA in our training test were always high, but decreased significantly in our test sets, highlighting the importance of cross-validation and regularization to avoid inflated results. Loadings of questionnaires corresponding to the circuit scores did not follow any interpretable pattern, with negative (e.g. fear) and positive (e.g. emotional support) scales often having comparable loadings for magnitude or sign. When considering connectivity, regions that are known to be implicated in emotion processing, such as the anterior cingulate cortex, insula, amygdala, temporal lobe and ventral striatum[6], showed the highest loadings. In a small preliminary sample from HCP-DES, we did not find any difference in circuit scores between patients and controls grouped by DSM diagnosis. However, in our clinical participants we found a significant correlation between self-reported stress and CS4, which in the original dataset primarily loaded on perceived stress and connectivity of the amygdala, insula, caudate and subgenual anterior cingulate cortex. Compatibly with the RDoC framework, this suggests that our circuit scores might be related to biological constructs underlying psychopathology that are not reflected in binary clinical diagnoses. Our project HCP-DES will expand on these preliminary results in a sample of 250 participants presenting with symptoms of anxiety and depression.