Reappraisal of Interpersonal Criticism in Social Anxiety Disorder:

A Brain Network Hierarchy Perspective

Supplemental Information

Supplemental Methods & Materials

Participants

Participants included 70 patients (32 females) with generalized SAD. All participants met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (Association 2013) criteria for a principal diagnosis of generalized SAD based on the Anxiety Disorders Interview Schedule for the DSM-IV: Lifetime Version (ADIS-IV-L). The control group consisted of 25 (13 females) demographically matched healthy subjects with no history of DSM-IV psychiatric disorders. This study was approved by the institutional review board at Stanford University, and all participants provided written informed consent. For more details on demographic and clinical variables see Ziv et al. 2013 (Ziv et al. 2013).

Clinical assessment

To assess social anxiety symptom severity, participants completed the Liebowitz Social Anxiety Scale-Self-Report (LSAS-SR) (Liebowitz 1987). This questionnaire assesses both fear and behavioral avoidance of social situations, and is widely used in the research of SAD (Fresco et al. 2001).

Trait measures of emotional regulation

To assess the participants' tendency to use reappraisal as an emotional regulation strategy, we used the emotional regulation questionnaire (ERQ) (Gross and John 2003). This questionnaire assesses individual differences in the use of two emotion regulation strategies: reappraisal and suppression. This is a 10-item questionnaire. Items are measured on a seven-point Likert scale, from 1 (strongly disagree) to 7 (strongly agree). This scale exhibits solid reliability of Cronbach's alpha for both reappraisal (0.79) and suppression (0.74).

fMRI data acquisition

Image acquisition and preprocessing: Image acquisition was performed on a General Electric 3-T Signa magnet with a T2*-weighted gradient echo spiral-in/out pulse sequence and a custom-built quadrature "dome" elliptical bird cage head-coil (GE Healthcare, Milwaukee, Wisconsin). Head movement was minimized using a bite-bar and foam padding. 684 functional volumes (2 scans x 342 TRs per scan) were obtained from 22 sequential axial slices (repetition time = 1500 milliseconds, echo time = 30 milliseconds, flip angle = 60°, field of view = 22 cm, matrix = 64x64, single-shot, resolution = 3.438 mm2 x 4.5 mm). Three- dimensional high-resolution anatomical scans were acquired using a fast spin-echo spoiled gradient recall (resolution = .8594 mm x 2 mm x 1.5 mm; field of view = 22 cm, frequency encoding = 256).

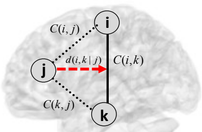
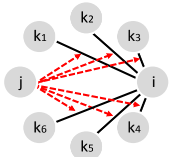
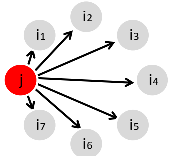
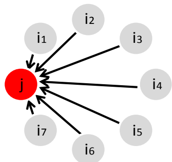
fMRI data preprocessing

fMRI data pre-processing was performed using Analysis of Functional Neuroimages (AFNI) software. Each functional run was subjected to preprocessing steps to maximize signal-to-noise contrast. To allow for T2* equilibration effects, the first four images of each functional run were excluded. In addition, signal preprocessing included an analysis of potential outliers, volume registration to a base image, motion correction, $4mm^3$ isotropic Gaussian spatial smoothing, high-pass filtering (.011 Hz), and linear detrending. Individual brain maps were converted to Talairach atlas space using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/). The two functional runs were concatenated prior to statistical analysis. No volumes demonstrated motion in the x, y, or z directions in excess of ±1 mm. There was no evidence of stimulus-correlated motion, as assessed by correlations between condition specific reference functions and x, y, z motion correction parameters. Finally, the average total global signal, which was calculated as the average across all voxels, was regressed out of every voxel time series.

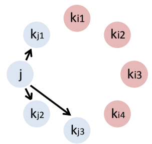
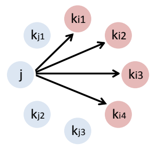
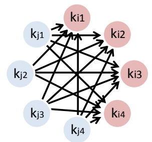
D_{EP}NA feature characteristics and interpretation

D_{EP}NA analysis (Jacob et al. 2016) provides a variety of measures ranging from a high resolution influence upon a single specific edge (i.e. correlation influence), to a broader region specific degree of influence (i.e. dependency matrix), a system level influence on an entire network (i.e. 'Influencing Degree' and 'Influenced Degree'), and up to a global level of influence of one network upon another (i.e. total inter-network influence). Each of these features can then be tested on different task conditions, groups, or in relation to individual behavioral measures. Table S1 represents our effort to summarize all D_{EP}NA measure characteristics and interpretations.

Table S1. Summary of D$_{EP}$NA measures- details and characteristics

D$_{EP}$NA measure	Definition	Characteristics	Interpretation
Correlation influence  $d(i,k\| j) \equiv C(i,k) - PartialCorr(i,k\| j)$	The influence of a specific region j signal on the correlation between a pair of different regions i and k signals. This measure is calculated according to the difference between the correlation C(i,k) and the partial correlation given j - PC(i,k|j).	• This quantity is large only when a significant fraction of the correlation between regions i and k signals can be explained in terms of region j.	• The correlation influence isa quantity of the effect a third node signal had over the correlation. • The 'correlation influence' measure is not a measure of correlation (i.e. co-linearity between two signals).
Dependency matrix  $D(i,j) = \frac{1}{N-1}\sum_{k \neq j}^{N-1} d(i,k\| j)$	The dependency matrix D(i,j) element is the influence of region j on region i. This measure is calculated as the average correlation influence of region j on the correlations of region i with all other regions k in the network C(i,k). In order to avoid cases when we sum over elements of different signs we sum over positive influences only.	• The dependency matrix is nonsymmetrical directed matrix since the influence of region j on region i is not equal to the influence of region i on region j.	• The dependency matrix allows for a directed graph of the brain network. • The dependency matrix measures do not infer causal influence in a true sense, rather infer the network' hierarchy of influence based on correlational influences.
Influencing Degree  Influencing Degree $(j) = \sum_{i \neq j}^{N-1} D(i,j)$	The total influence of region j on the entire network. This measure is quantified as the sum of the influences D(i,j) of j on all other regions i.	• Provide the hierarchy of efferent (output) influence on the network. • The higher the region's 'Influencing Degree' the more it influenced all other connections in the network.	• Regions with a high 'Influencing Degree' are more likely to generate the cognitive process. • The longer the region processes the information (sustained activation), the higher it's influence on the entire network.
Influenced Degree  Influenced Degree $(j) = \sum_{i \neq j}^{N-1} D(j,i)$	The total influence of the entire network on the specific region j. This measure is quantified as the sum of all the influences D(j,i) of all regions i in the network on region j.	• Provide the hierarchy of afferent (input) influence by the network. • The higher the region's 'Influenced Degree' the more it was dependent or influenced by all the other regions in the network.	• The further downstream the node is in the network, the higher its 'Influenced Degree', however, it was found to be very sensitive to the SNR. • Regions with a high 'Influenced Degree' are more likely to be simultaneously influenced by many other regions. • An increased 'Influenced Degree' pattern compared to baseline of the entire network indicates network's integration (i.e. all regions are more influenced by all other regions). • A decreased 'Influenced Degree' pattern indicates network segregation.

Summary of DEPNA measures- details and characteristics (Continued)

DEPNA measure	Definition	Characteristics	Interpretation
Intra-network influence  $Influencing\ Degree_{Intra}(j)=\sum_{kj}^{Nkj} D(kj,j)$	The total influence of region j on the entire sub-network to which it belongs. This measure is quantified as the sum of the influences D(kj,j) of region j on all other regions kj within the Kj network.	• Provide the hierarchy of afferent (input) influence within the sub-network. • The higher the region's intra-network influence degree the more it influenced all other connections within its sub-network.	• Same as 'Influencing Degree' only within a smaller sub-network.
Inter-network influence  $Influencing\ Degree_{Inter}(j)=\sum_{i}^{Nki} D(ki,j)$	The total influence of region j on different sub-network regions. This measure is quantified as the sum of the influences D(ki,j) of region j on all other regions ki within the Ki network.	• Provide the hierarchy of efferent (output) influences of regions from one sub-network only on the connections of different sub-network regions. • The higher the region's inter-networks influence degree the more it influenced all other connections within the other sub-network and between the two sub-networks.	• Regions with a high inter-network influence are more likely to integrate between the two networks.
Total inter-networks influence  $Total\ \ Inter-Network(Kj)=\sum_{kj}^{Nkj}\sum_{ki}^{Nki} D(ki,kj)$	The total influence of sub-network Kj on sub-network Ki. This measure is quantified as the sum of all the influences D(ki,kj) of all kj regions within the Kj sub-network on all regions ki within the Ki sub-network.	• This quantity is large only when a significant fraction of the correlation between regions i and k signals can be explained in terms of region j.	• The 'correlation influence' measure is not a measure of correlation (i.e. co-linearity between two signals), rather a quantity of the effect a third node signal had over the correlation.

Supplemental Results

D_{EP}NA inter-network influences during watch criticism condition

The reappraisal network exhibited less influence on the reactivity network among SAD patients relative to HCs during the reappraise condition. Here as a control we wanted to assess whether this lesser influence accurse also during the watch condition. We applied the D_{EP}NA influencing index on the inter-network influence and total inter-network influence during the watch criticism condition.

The regional inter-network as well as the total inter-network analyses found no significant differences between SAD and HC during the watch condition (Figure S1).

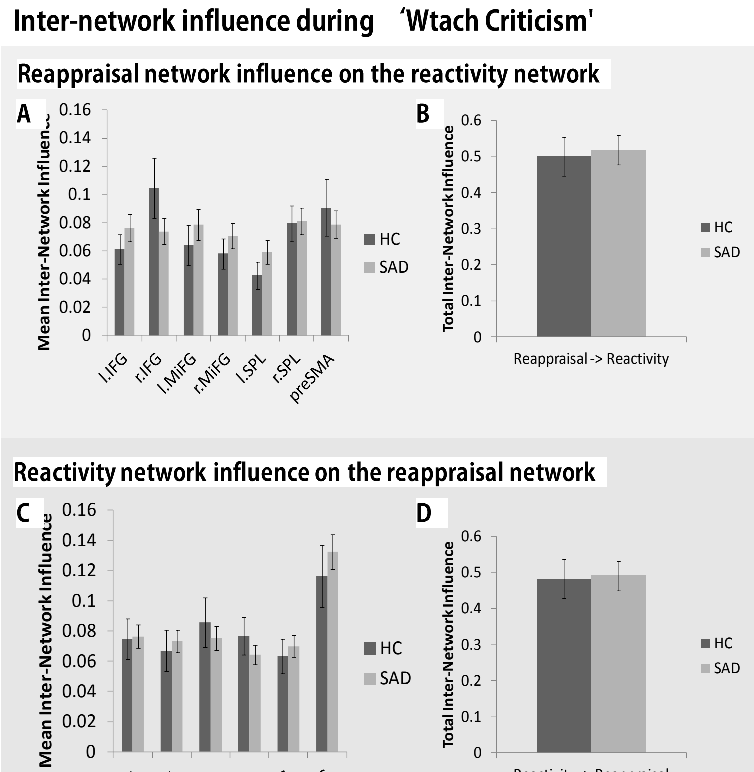


Figure S1. Control DEPNA inter-network analysis during the watch criticism condition. The regional influence of the cognitive reappraisal network regions on the emotional reactivity network **(A)** and the total cognitive reappraisal network on the emotional reactivity network **(B)**. The regional influence of the emotional reactivity network regions on the cognitive reappraisal network **(C)** and the total emotional reactivity network on the cognitive reappraisal network **(D)**. The results are averaged across all 70 SAD patients and 25 healthy controls. As expected, none of these analyses were found to be significantly different between the groups during the watch criticism condition.

Control 'Asterisks' condition $D_{EP}NA$ analysis

An asterisk-counting task was used as a control condition (16 trials of 12 sec), during which subjects were asked to press a button to indicate the number of asterisks on the screen which changed every 3 seconds and varied from 1 to 5 asterisks.

In order to further validate our results we conducted intra- and inter-network $D_{EP}NA$ on the third asterisks control condition in which no differences between the groups were expected. We then conducted for each network a between-group t-test for each region's *'Influencing Degree'* and corrected for multiple comparisons using the FDR.

As expected, $D_{EP}NA$ found no significant differences in the *'Influencing Degree'* between the two groups during the asterisks condition (Figure S2).

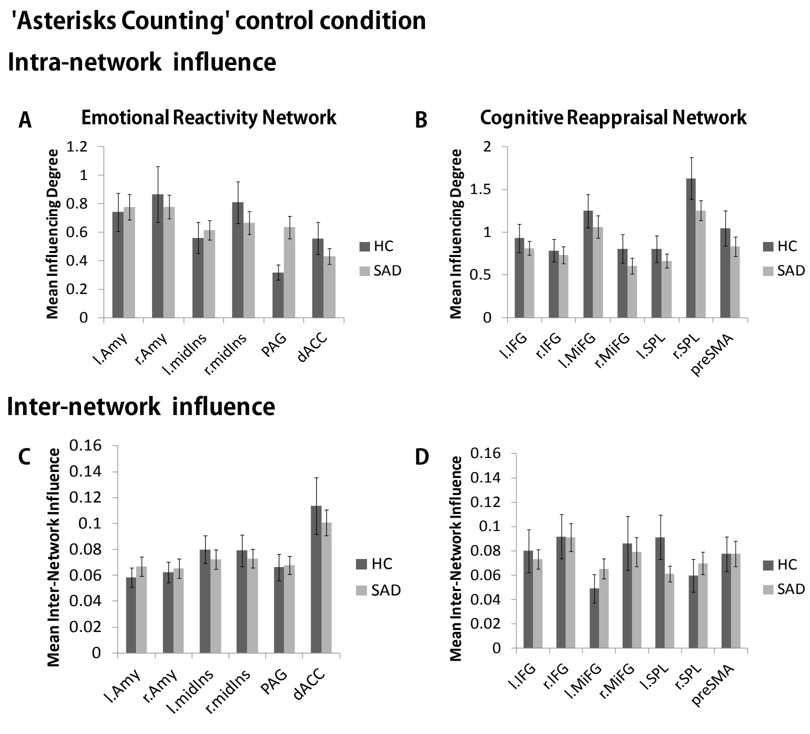


Figure S2. Control 'Asterisks' condition results. Intra-network analysis of the emotional reactivity network **(A)**, and cognitive reappraisal network **(B)** *'Influencing Degree'*. The inter-network analysis of the emotional reactivity regions' influence on the cognitive reappraisal network **(C)**, and the cognitive reappraisal regions' influence on the emotional reactivity network **(D)** *'Influencing Degree'*. The results are averaged across all 70 SAD patients and 25 healthy controls. As expected, none of the regions were found to be significantly different between the groups during the 'Asterisks' condition.

Control Study - motor network $D_{EP}NA$ analysis

In addition, we conducted the identical $D_{EP}NA$ analysis on the reappraise and watch conditions, only on a different brain network. We chose to look at a motor network as it is not task related in any manner.

We extracted the motor network, which included a set of regions that are consistently activated during hand or foot movements (Biswal et al. 1995; Shirer et al. 2012). Overall the motor network consisted of 6 regions of interest (ROIs), and these ROIs were defined according to the Wake Forest University (WFU) PickAtlas (Maldjian et al. 2003). The averaged BOLD signal (time series) was then extracted for each ROI mask image and each subject.

As expected, $D_{EP}NA$ found no significant differences in the *'Influencing Degree'* within the motor network either during the watch or the reappraise conditions (Figure S3).

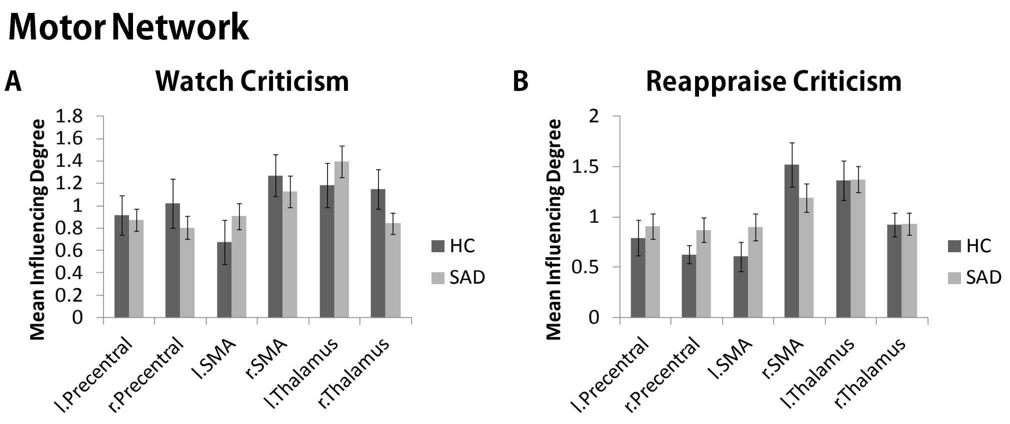


Figure S3. Control motor network results. The motor network regions' *'Influencing Degree'* averaged across all 70 SAD patients and 25 healthy controls during the watch criticism condition **(A)**, and during the reappraise criticism condition **(B)**. As expected, none of the regions was found to be significantly different between the groups within the control motor network regions.

Supplemental References

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