

## Reconfiguration of brain networks supporting inhibition of emotional challenge



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### ABSTRACT

Reacting to the salient emotional features of a stimulus is adaptive unless the information is irrelevant or interferes with goal-directed behavior. The ability to ignore salient but otherwise extraneous information involves restructuring of brain networks and is a key impairment in several psychological disorders. Despite the importance of understanding inhibitory control of emotional response, the associated brain network mechanisms remain unknown. Utilizing functional magnetic resonance imaging (fMRI) data obtained from 103 participants performing an emotion-word Stroop (EWS) task, the present study applied graph-theory analysis to identify how brain regions subserving emotion processing and cognitive control are integrated within the global brain network to promote more specialized and efficient processing during successful inhibition of response to emotional distractors. The present study identified two sub-networks associated with emotion inhibition, one involving hyper-connectivity to prefrontal cortex and one involving hyper-connectivity to thalamus. Brain regions typically associated with identifying emotion salience were more densely connected with the thalamic hub, consistent with thalamic amplification of prefrontal cortex control of these regions. Additionally, stimuli high in emotional arousal prompted restructuring of the global network to increase clustered processing and overall communication efficiency. These results provide evidence that inhibition of emotion relies on interactions between cognitive control and emotion salience sub-networks.

### 1. Introduction

Emotional information is often highly salient and has a profound and immediate impact on attention. For instance, highly arousing stimuli narrow attentional scope (Gable and Harmon-Jones, 2010), aversive stimuli draw attention to finer details of a scene, and pleasant stimuli broaden attention to the overall scene (Gasper and Clore, 2002). Although these adaptations often serve to direct attention to potentially lifesaving cues, emotional information that is not goal-relevant can draw attention away from the task at hand and thus impair performance. Disorders such as depression and anxiety are characterized by maladaptive failures to inhibit goal-irrelevant emotional processing, resulting in an increased attentional bias toward negative and highly arousing information and away from goal-relevant responding (Dai and Feng,

2011; Levin et al., 2007; Williams et al., 1996). Achieving a better understanding of this chronic bias requires knowledge of how brain networks supporting inhibition are altered when distracting emotional information must be inhibited.

Automatic down-regulation of an incorrect prepotent response in favor of the task-appropriate response is conceptualized as inhibitory control. Recent evidence obtained with the color-word Stroop (CWS) task suggests that successful inhibitory control is associated with dynamic reorganization of the global neural network to prevent salient but task-irrelevant stimuli from interfering with cognitive processing (Spielberg et al., 2015). During the CWS, inhibitory mechanisms are engaged to facilitate ignoring the color information contained in the meaning of a word in order to identify the color of the ink in which the word is printed. Thus, even a simple form of inhibition is a complex process supported by

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a network of brain regions, including frontal, parietal, and subcortical regions (e.g., [Spielberg et al., 2015](#), [Banich et al., 2009](#)).

Applying graph theory methods to the global brain network engaged during performance of the CWS, [Spielberg et al. \(2015\)](#) determined that higher demand for inhibitory control was associated with reorganization of brain regions within the global network. This reorganization led to a network configuration that was optimized for integrating information across brain regions (as indexed by higher levels of the graph property ‘Global Efficiency’) and for engaging in specialized processes (higher ‘Transitivity’), and was more resilient to disruption (higher ‘Assortativity’). In addition to the overall organization and structure of the global network, graph theory can be used to elucidate the role that a single region or connection plays in the larger network. Several inhibitory-control-related regions emerged as being crucial network nodes for adaptive task performance during the CWS, including left inferior frontal sulcus (IFS), right anterior insula, and dorsal anterior cingulate cortex (dACC; [Spielberg et al., 2015](#)). Thus, successful cognitive control appears to result, in part, from engaging prefrontal regions as one or more central network hubs.

Despite evidence suggesting that inhibitory control regions should interact with emotion salience regions during inhibition of response to emotional stimuli, the dynamic nature of such interactions is unknown. Tasks that utilize exposure to salient yet irrelevant and distracting emotional stimuli often draw on brain regions associated with stimulus-driven attentional processing (e.g., [Hariri et al., 2000](#); [Ochsner and Gross, 2005](#)). In the case of emotionally salient stimuli, regions implicated in emotional processes such as amygdala – which has been widely associated with processing stimulus-driven salience – would presumably be incorporated into the network supporting inhibition (e.g., [Compton et al., 2003](#); [Garcia-Garcia et al., 2016](#)). Similarly, posterior areas related to emotion recognition, such as posterior parietal and occipito-temporal regions ([Compton et al., 2003](#)), and regions involved in affective memory reconstruction, including hippocampus ([Compton et al., 2003](#); [Sadeh et al., 2014](#)), are likely to be more active in the network during the inhibition of emotionally salient information. Thus, a network of brain regions involving IFS and ACC, supporting goal-driven inhibition processes, and a network comprised of amygdala, hippocampus, posterior parietal, and occipito-temporal regions, supporting stimulus-driven processing of emotion, are hypothesized to participate in the interplay between inhibition and emotion processing systems. To probe this hypothesis, a variant of the CWS was used wherein the distracting, goal-irrelevant information is affective in nature, rather than color-related. This allowed for the assessment of inhibition of responses to emotional stimuli. The emotion-word Stroop task (EWS; [Dalgleish and Watts, 1990](#), [Mohanty et al., 2007](#), [Williams et al., 1996](#)) relies on inhibition of the response to the affective content of the word meaning (positive, neutral, or negative) to facilitate accurate identification of word color.

There is compelling evidence that this EWS accesses emotion processing and subsequent inhibition. The emotional content of the word instantiates reactivity in limbic networks of the participant ([Compton et al., 2003](#); [Sadeh et al., 2014](#); [Feng et al., 2018](#)). This reactivity includes attentional orienting to the emotional stimuli and engagement with/processing of the distracting emotional content. This distraction has been demonstrated via a significant increase in reaction time that is commonly associated with emotion words ([Compton et al., 2003](#); [Koven et al., 2003](#)). Goal-oriented performance in the EWS is responding as quickly as possible to the color of the word on the screen. Engaging with emotional stimuli depletes attention and detracts from performance of the goal-oriented response. Therefore, successful (fast) performance in the EWS necessitates down-regulation of the prepotent response (engagement of emotional content) in favor of the goal-oriented response (in this case, processing word color).

In summary, the present study sought to identify mechanisms by which brain networks restructure to support critical down-regulation of goal-irrelevant responses to emotional challenge. Discovering these

mechanisms will help to clarify how inhibition contributes to emotion regulation and how failures in emotion inhibition foster risk for psychopathology. We predicted that IFS would remain a central sub-network hub supporting inhibition, regardless of the prepotent response to be inhibited. Due to the emotional salience of the task-irrelevant stimuli, we expected that the EWS task would draw more posterior parietal and limbic nodes into the functional sub-network involving IFS in order to minimize emotion-related distraction and facilitate cognitive task completion ([Compton et al., 2003](#); [Beauregard et al., 2001](#)).

## 2. Material and methods

Participants in this study were recruited using newspaper and online advertisements, provided informed written consent in compliance with a protocol approved by the University of Illinois Institutional Review Board, and were paid for their time.

### 2.1. Participants

Data were collected from 133 participants recruited from the community as part of a larger project at the University of Illinois at Urbana-Champaign. Participants were screened and excluded for claustrophobia, left-handedness, prior serious brain injury, abnormal hearing/vision, neurological disorders, metal in body, pregnancy, and nonnative English. They completed the CWS task, which was reported in [Spielberg et al. \(2015\)](#), and the EWS task during the same MRI session, with task order counterbalanced. Participants were excluded from the present study (i) if  $\geq 3.3$  mm of movement was detected relative to the middle volume of a run or  $\geq 2.0$  mm of movement was detected relative to the previous volume ( $n = 4$ ), (ii) if they committed errors on  $\geq 10\%$  of trials or exhibited reaction times (RTs)  $\geq 3$  SD from the sample mean ( $n = 8$ , meeting both error and RT criteria), (iii) if they displayed susceptibility artifact in areas of importance or motion artifacts ( $n = 4$ ), or (iv) due to errors in MRI ( $n = 4$ ) or behavioral acquisition ( $n = 4$ ) or other technical issues associated with task completion ( $n = 6$ ). The remaining 103 participants (see [Table 1](#) for demographic information) were included in all subsequent analyses. Pearson correlations were performed to assess relationships between age, gender, level of education, and RT. Although effects of interest were within-subject rather than between-subject, the possibility of developmental or education level effects remains. Age was found to be correlated with RT in every condition ( $r = 0.22$  to  $0.26$ ,  $p < 0.05$ ), and education level was related to percent errors ( $r = -0.31$ ,  $p = 0.01$ ) ([Table 2](#)). Therefore, these variables were entered into a network analysis as predictors. As no significant associations were found, age and education level were not included in subsequent analyses ([Miller and Chapman, 2001](#); [Verona and Miller, 2015](#)).

**Table 1**  
Demographic information and behavioral performance.

	Mean	Standard Deviation
Age	35 years	9 years
Gender	61% Female	
Education	17 years	2 years
Positive Trial RT	700 ms	97 ms
Neutral Trial RT	701 ms	97 ms
Negative Trial RT	716 ms	99 ms
Positive Trial Percent Error	4.40%	2.50%
Neutral Trial Percent Error	3.05%	2.30%
Negative Trial Errors	4.86%	2.84%
Positive Trial IES	731 ms	104 ms
Neutral Trial IES	722 ms	101 ms
Negative Trial IES	752 ms	108 ms

Notes: Reaction time (RT) during negative trials was slower than RT during positive and neutral trials, which did not differ from each other. Errors during neutral trials were lower than errors in positive and negative trials, which did not differ from each other.

**Table 2**

Correlations between demographic variables, reaction time (RT), and percent errors.

Age	–		
Gender	–0.08	–	
Education	0.11	0.12	–
Positive RT	0.22*	0.06	–0.04
Neutral RT	0.25*	0.01	–0.04
Negative RT	0.26**	–0.03	–0.01
Percent Errors	–0.06	0.07	–0.12

Notes: \* indicates significance at the  $p \leq 0.05$  level (2-tailed). \*\* indicates significance at the  $p \leq 0.01$  level (2-tailed). Percent errors are overall task errors.

Connectivity matrices are available upon request.

## 2.2. Emotion-word Stroop task

Sixteen blocks of 16 trials provided 256 trials. Stimuli were blocked by word type (four positive, eight neutral, four negative blocks). Each trial consisted of one word presented in one of four ink colors, with each color occurring equally often with each word type. Within a variable onset-to-onset intertrial interval of  $2000 \pm 225$  ms, a 1500 ms word presentation was followed by a  $500 \pm 225$  ms fixation cross. Words were selected based on standardized ratings of valence and arousal (Bradley and Lang, 1998). For negative valence trials, words were selected if they were rated as negative in valence and high in arousal (valence:  $M = 1.65$ ,  $SD = 0.74$ ; arousal:  $M = 5.46$ ,  $SD = 1.51$ ). For positive trials, words were selected if they were rated as positive in valence and high in arousal (valence:  $M = 5.77$ ,  $SD = 1.14$ ; arousal:  $M = 5.80$ ,  $SD = 1.46$ ). Neutral words were selected if they were near average on ratings of both scales and matched one of the emotion words for concreteness, imageability, familiarity, and length (valence:  $M = 3.93$ ,  $SD = 0.72$ ; arousal:  $M = 2.16$ ,  $SD = 0.65$ ). Prior to completing the task, participants were instructed to indicate the color of the word presented on the screen by pressing one of four buttons. Participants were instructed to ignore word meaning.

## 2.3. Acquisition

High-resolution ( $1 \text{ mm}^3$ ) MPRAGE structural magnetic resonance imaging brain scans consisting of 160 slices ( $TR = 1700$  ms,  $TE = 3.5$  ms,  $TI = 900$  ms, resolution =  $1 \text{ mm}^3$ ) were acquired for each participant. fMRI consisted of 370 EPI images (duration = 12.33 min,  $TR = 2000$  ms,  $TE = 25$  ms, flip angle =  $80^\circ$ ) acquired on a Siemens 3T Trio scanner. Each image consisted of 38 axial slices (slice thickness = 3 mm, 0.3 mm gap, in-plane resolution =  $3.4375 \times 3.4375$  mm).

## 2.4. Data preprocessing

Preprocessing was conducted using FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>), the Graph Theory GLM (GTG) MATLAB toolbox ([www.nitrc.org/projects/metalab\\_gtg](http://www.nitrc.org/projects/metalab_gtg)), and AFNI ([afni.nimh.nih.gov/](http://afni.nimh.nih.gov/)). Preprocessing consisted of motion correction using 6 standard motion parameters and field-map correction via FSL, despiking via AFNI, application of a temporal Butterworth high-pass filter (0.01 Hz), second-order temporal detrending, and partialling of each participant's mean global signal, motion parameters, and mean white matter and ventricular signals. White-matter and ventricular masks were created for each participant via FSL's FAST.

## 2.5. Connectivity matrices

Network nodes were defined using a 184-region brain atlas developed by Shen and colleagues (Shen et al., 2013). Time-series data were extracted from each region of interest (ROI) as the mean across voxels in an ROI for each time point. Extracted time-series were quality-checked for irregularities (e.g. motion-related artifacts). ROIs were excluded

from time-series extraction if the segmentation included fewer than 5 voxels or less than 25% of the voxels with the ROI. Eight ROIs, with insufficient coverage in cerebellum for a large subset of participants, were excluded, resulting in extracted time-series data for 176 ROIs. All 103 participants maintained complete time series data after these eight ROIs were removed and were therefore retained for analysis.

Time series for each ROI were deconvolved with a canonical HDR function, and then time series were divided by task block. Blocks were then concatenated by condition (positive, neutral, or negative words), and time series between each pair of ROIs were correlated (within participant and task condition) using a robust Pearson correlation technique that down-weights or removes marginal or bivariate outliers (Pernet et al., 2013). This created three  $176 \times 176$  robust correlation matrices for each participant (i.e., one matrix per condition). As previous work has demonstrated that this analysis method ensures that mean differences in signal across conditions cannot drive effects (Spielberg et al., 2015), variance related to task condition was not regressed out in these analyses.

## 2.6. Identification of network connections related to emotion inhibition

To identify network elements that varied as a function of emotion inhibition, connectivity matrices were entered into the Network Based Statistic (NBS; [www.nitrc.org/projects/nbs/](http://www.nitrc.org/projects/nbs/)) toolbox using task condition as a repeated measure. In NBS, connectivity matrices are entered as dependent variables, and the regression model is tested for each link, following which a  $t$ -threshold is applied to each link across the network to remove weakly/unassociated links. As there is currently no accepted way to determine an optimal or appropriate threshold for these analyses, multiple thresholds were examined to ensure that the results were consistent across thresholds. A threshold of  $t = 3.2$  was chosen, as it resulted in stable networks across findings. Next, clusters of supra-threshold links (i.e., links sharing a node with  $\geq 1$  other links) are identified, and the corrected significance of each cluster is computed. The cluster-extent-corrected  $p$ -value is calculated by comparing observed cluster size (number of links) against a null distribution of maximal supra-threshold sizes created via permutation (5000 randomizations), resulting in an overall corrected  $\alpha < 0.05$ .

Two orthogonal contrasts were tested in the NBS model, capturing valence and arousal qualities of emotion (Posner et al., 2005). A within-subject linear contrast compared positive and negative conditions, capturing the valence effect. A within-subject quadratic contrast comparing the combination of positive and negative trials against neutral trials captured the arousal effect. Contrasts modeling each participant's individual mean were included in order to model each participant's mean individually, as is required for a repeated-measures analysis.

## 2.7. Identification of graph-theory properties related to emotion inhibition

The GTG toolbox was used to identify topological properties that differed by emotion inhibition condition. GTG was used to calculate 11 graph-theory properties (Global Efficiency, Transitivity, Assortativity, Local Assortativity, Local Efficiency, Brokerage, Closeness Centrality, and Participation Coefficient).

These properties were selected based on consistency with previous work on network restructuring in the color-word Stroop task (Spielberg et al., 2015) and their relevance to understanding how the overall structure of a network functions and how individual regions change their relationship to the network in response to changing task demands, a primary aim of the present study. Global properties such as Global Efficiency, Transitivity, and Assortativity were selected because they index efficiency of moving information between regions of a network, specialized processing within a network, and the tendency for a network to have backup hubs in case of disturbance or disruption of a primary hub, respectively (Bullmore and Sporns, 2009).

The remaining local graph properties assess the relationship that a

particular node has to other nodes in its cluster, characterize the movement of information across the network, and provide important information about how the role of a region and its relationship to neighboring structures change dynamically with task demands (Bullmore and Sporns, 2009). Like their global counterparts, Local Assortativity and Local Efficiency assess the extent to which a node is connected to other highly connected nodes and the efficiency of communication amongst the nodes neighbors, respectively. Similarly, Brokerage assesses the extent to which a node represents a shortcut or important bridge between clusters. Closeness Centrality and Participation Coefficient assess how tightly connected a region is to all other regions in a network and to other clusters, respectively. Detailed information on how these properties are calculated can be found in the documentation for the GTG toolbox, which is freely available ([www.nitrc.org/projects/metalab\\_gtg](http://www.nitrc.org/projects/metalab_gtg)).

First, matrices were thresholded to include only positive weights and normalized via division by median weight (excluding zeros) per matrix. Unlike some studies that use higher (and often multiple) density thresholds and binarize the networks, only one threshold (zero) and retained link weights were used because this method retains important information about the weighted networks (Rubinov and Sporns, 2010). The zero threshold was used because positive and negative weights are typically analyzed separately (Rubinov and Sporns, 2010), and weight normalization was performed, in part, to account for potential bias introduced by thresholding.

Properties were calculated separately for each task condition and then subjected to a permutation analysis using contrasts for task conditions, which results in a  $\beta$  statistic subjected to an F-test. The properties listed above were chosen based on their relevance to the quantification of network structure and efficiency and based on their inclusion in the CWS study of Spielberg et al. (2015). In order to limit the number of comparisons, properties were examined only for the nodes identified in the NBS analysis as having the highest number of connections in that network. Four nodes were selected for graph property analysis. Relationships were tested only for predictors significant in the equivalent NBS analysis.

### 3. Results

#### 3.1. Overt performance

As a manipulation check, the effects of condition (positive, neutral, or negative word) on RT and percent errors were examined (Table 1). With condition as a within-subject factor in a repeated-measures ANOVA, valence and arousal appeared to contribute to the relationship between RT and condition ( $F_{(2,91)} = 10.02$ ,  $p < 0.001$ ,  $\eta^2 = 0.10$ , Huynh-Feldt epsilon = 0.95), demonstrated by the linear contrast ( $F_{(1,91)} = 12.28$ ,  $p = 0.001$ ,  $\eta^2 = 0.12$ ) and the quadratic contrast ( $F_{(1,91)} = 15.60$ ,  $p = 0.02$ ,  $\eta^2 = 0.06$ ). RT was slower during negative trials than during positive trials ( $t_{(91)} = 3.50$ ,  $p = 0.001$ , 95% CI [6.85, 24.77]) and neutral trials ( $t_{(91)} = -4.18$ ,  $p < 0.001$ , 95% CI [-22.58, -8.04]). However, RT did not differ significantly between positive and neutral trials ( $t_{(91)} = -0.131$ ,  $p = 0.896$ , 95% CI [-8.10, 7.10]). Arousal contributed to the relationship between accuracy (calculated as % of errors) and condition ( $F_{(2,91)} = 19.06$ ,  $p < 0.001$ ,  $\eta^2 = 0.17$ , epsilon = 0.95), demonstrated by the quadratic contrast ( $F_{(1,91)} = 39.68$ ,  $p < 0.001$ ,  $\eta^2 = 0.30$ ). Specifically, accuracy was lower for both positive trials ( $t_{(91)} = 4.24$ ,  $p < 0.001$ , 95% CI [0.01, 0.02]) and negative trials ( $t_{(91)} = -6.50$ ,  $p < 0.001$ , 95% CI [-0.02, -0.01]) than for neutral trials. Accuracy did not differ significantly between positive and negative trials ( $t_{(91)} = 1.55$ ,  $p = 0.13$ , 95% CI [-0.001, 0.01]).

Due to the difference in pattern observed for RT and arousal, inverse efficiency scores (IES; Townshend and Ashby, 1978) were calculated. IES integrates RT and accuracy in order to account for a potential tradeoff in performance between speed and accuracy. Valence and arousal appeared to contribute to the relationship between IES and condition ( $F_{(2,91)} = 18.22$ ,  $p < 0.001$ ,  $\eta^2 = 0.167$ , Huynh-Feldt epsilon = 0.95),

demonstrated by the linear contrast ( $F_{(1,91)} = 15.60$ ,  $p < 0.001$ ,  $\eta^2 = 0.146$ ) and the quadratic contrast ( $F_{(1,91)} = 21.48$ ,  $p < 0.001$ ,  $\eta^2 = 0.191$ ), which capture valence and arousal effects, respectively. IES was smaller during both negative trials than during neutral trials ( $t_{(91)} = -6.64$ ,  $p < 0.001$ , 95% CI [-38.38, -20.70]) and positive trials ( $t_{(91)} = 3.95$ ,  $p < 0.001$ , 95% CI [10.40, 31.44]). IES did not differ significantly between positive and neutral trials ( $t_{(91)} = 1.55$ ,  $p = 0.13$ , 95% CI [-0.001, 0.01]).

#### 3.2. Network-based-statistic identification of networks sensitive to emotion inhibition

Analyses revealed three sub-networks of regions exhibiting differential connectivity as a function of valence. As illustrated in Fig. 1, one network evidenced stronger connectivity to positively than negatively valenced stimuli ( $p_{corrected} = 0.01$ ,  $\eta^2 = 0.337$ ; 10 nodes, 9 links). Angular gyrus, cingulate gyrus, parahippocampal gyrus, and frontal pole had the highest number of differential links.

The two other sub-networks showed the opposite effect, with more connectivity during negative than positive valence trials. In the second sub-network (Fig. 2;  $p_{corrected} = 0.002$ ,  $\eta^2 = 0.564$ ; 15 nodes, 16 links), IFG was connected to the right frontal pole, and each was connected to several temporo-parietal regions and left parahippocampal gyrus. In the third sub-network (Fig. 3) ( $p_{corrected} = 0.004$ ,  $\eta^2 = 0.38$ ; 11 nodes, 10 links), left thalamus was connected to prefrontal cortex and occipito-temporal regions. No significant findings emerged for the arousal contrast.

#### 3.3. 3 global network properties associated with emotion inhibition

##### 3.3.1. Valence effects

No significant change in global network properties was associated with the valence of stimuli to be inhibited.

##### 3.3.2. Arousal effects

The global network showed greater overall network segregation (i.e. Transitivity, or clustering into separate groups of nodes) for high, relative to low, arousal stimuli ( $F = 213.77$ ,  $p < 0.001$ ,  $\eta^2 = 0.68$ ). Additionally, the global network was associated with greater overall network integration (i.e. Global Efficiency, or efficiency of information transfer) for high-arousal stimuli ( $F = 1231.81$ ,  $p < 0.001$ ,  $\eta^2 = 0.92$ ). High levels of both segregation and integration are indicative of a small world organization, which is a particularly efficient overall network structure (Bullmore and Sporns, 2009). Assortativity of the global network did not change as a function of the arousal of the stimuli to be inhibited.

#### 3.4. Local network properties associated with emotion inhibition

Based on the emergent networks reported above (Figs. 1–3), nodes demonstrating the greatest number of connections across networks were included in further analysis. These nodes were selected for graph property assessment and their properties entered into a repeated-measures general linear model, testing effects of valence and arousal on graph properties. Nodes included left IFG, left thalamus, right precuneus, and left insula. Results are summarized in Table 3.

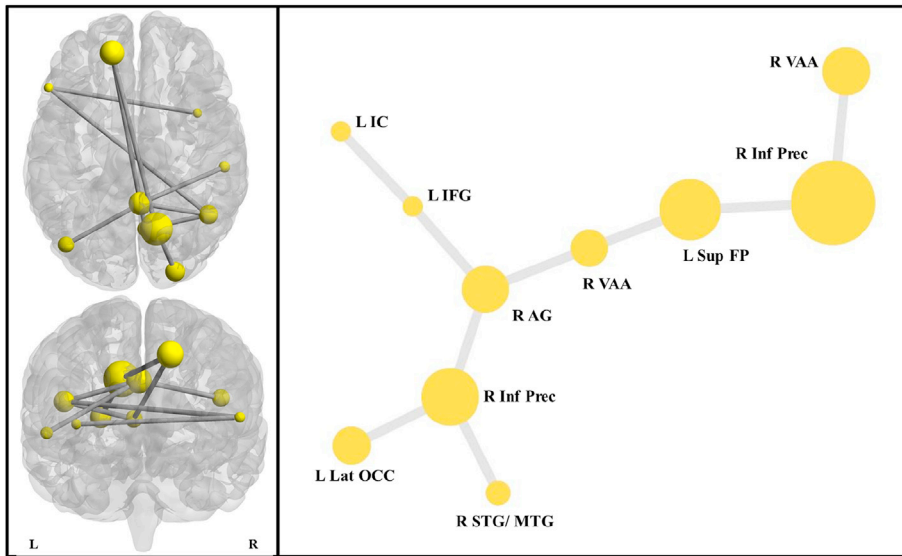
##### 3.4.1. Valence effects

As valence of the emotional stimuli became more negative, the Participation Coefficient of precuneus increased ( $F = 9.46$ ,  $p_{FDR\ corrected} = 0.038$ ,  $\eta^2 = 0.08$ ). Specifically, precuneus maintained more functional connections to other modules (clusters of densely connected nodes) during negative word trials than during positive word trials.

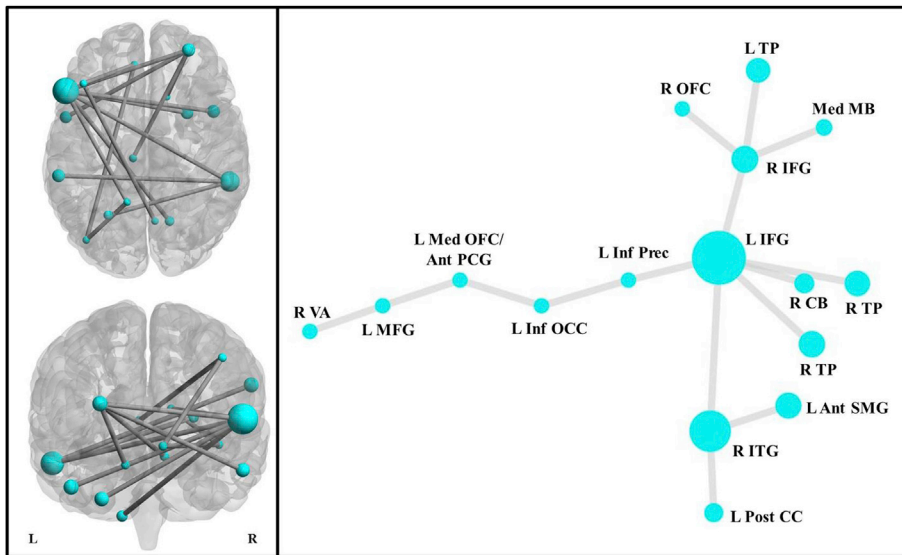
##### 3.4.2. Arousal effects

Extent of local clustering or segregation was assessed via Local Efficiency. IFG ( $F = 102.18$ ,  $p_{FDR\ corrected} < 0.001$ ,  $\eta^2 = 0.50$ ), precuneus





**Fig. 1.** Network configuration showing stronger connectivity during positive than during negative word ( $p = 0.01$ ). Thresholding significant comparisons at  $t = 3.2$ . In this and subsequent figures, node size indicates mean node strength across participants. Results in this and subsequent figures are plotted on smoothed MNI ICBM152 brains. Areas included in the network are as follows: 1) right angular gyrus, 2) right inferior precuneus, 3) right visual association area, 4) right inferior precuneus, 5) right visual association area, 6) right STG/MTG, 7) left IFG, 8) left insular cortex, 9) left superior frontal pole, 10) left lateral occipital cortex.



**Fig. 2.** First network configuration that increases in strength during negative relative to positive words ( $p = 0.002$ ). Thresholding significant comparisons at  $t = 3.2$  and significant networks at  $p = 0.05$ . Areas included in the network are as follows: right inferior frontal pole, R Inf FP; right temporal pole, R TP; right cerebellum, R CB; right inferior temporal gyrus, R ITG; right orbitofrontal cortex, R OFC; right visual association area, R VA; right temporal pole, R TP; left medial frontal gyrus, L MFG; left inferior frontal gyrus, L IFG; left anterior supramarginal gyrus, L Ant SMG; left inferior occipital cortex, L Inf OCC; left posterior cingulate cortex, L Post CC; left inferior precuneus, L Inf Prec; left temporal pole, L TP; medial midbrain, Med MB; left medial orbitofrontal cortex/left anterior postcentral gyrus, L Med OFC/Ant PCG.

( $F = 111.62$ ,  $p_{FDR \text{ corrected}} < 0.001$ ,  $\eta^2 = 0.52$ ), insular cortex ( $F = 130.23$ ,  $p_{FDR \text{ corrected}} < 0.001$ ,  $\eta^2 = 0.56$ ), and thalamus ( $F = 108.80$ ,  $p_{FDR \text{ corrected}} < 0.001$ ,  $\eta^2 = 0.52$ ) evidenced greater Local Efficiency in response to higher arousal stimuli. Thus, the neighbors of these nodes showed greater clustering with each other in order to increase efficiency of information transfer during emotion-challenge trials relative to neutral trials.

Local integration of information transfer was assessed via Brokerage. Nodes in IFG ( $F = 16.80$ ,  $p_{FDR \text{ corrected}} < 0.001$ ,  $\eta^2 = 0.14$ ), thalamus ( $F = 17.17$ ,  $p_{FDR \text{ corrected}} = 0.01$ ,  $\eta^2 = 0.14$ ), and precuneus ( $F = 17.17$ ,  $p_{FDR \text{ corrected}} < 0.001$ ,  $\eta^2 = 0.14$ ) demonstrated reduced Brokerage during high-arousal trials, suggesting that high-arousal trials degraded reliance on these nodes as hubs of communication between networks.

High-arousal trials also fostered increased Closeness Centrality of nodes in IFG ( $F = 249.60$ ,  $p_{FDR \text{ corrected}} < 0.001$ ,  $\eta^2 = 0.71$ ), precuneus ( $F = 302.73$ ,  $p_{FDR \text{ corrected}} < 0.001$ ,  $\eta^2 = 0.75$ ), insular cortex ( $F = 235.76$ ,  $p_{FDR \text{ corrected}} < 0.001$ ,  $\eta^2 = 0.70$ ), and thalamus ( $F = 183.23$ ,  $p_{FDR \text{ corrected}} < 0.001$ ,  $\eta^2 = 0.64$ ). This indicates that emotional distractors prompted shorter distances between, or more direct connections

linking, these nodes and all other nodes.

Emotional distractors increased Participation Coefficient for nodes in inferior frontal gyrus ( $F = 102.18$ ,  $p_{FDR \text{ corrected}} = 0.006$ ,  $\eta^2 = 0.50$ ;  $F = 162.89$ ,  $p_{FDR \text{ corrected}} < 0.001$ ,  $\eta^2 = 0.61$ ), precuneus ( $F = 111.62$ ,  $p_{FDR \text{ corrected}} < 0.001$ ,  $\eta^2 = 0.52$ ), and thalamus ( $F = 108.80$ ,  $p_{FDR \text{ corrected}} < 0.001$ ,  $\eta^2 = 0.52$ ). Thus, these nodes increased connections to other modules in the network when distractors were high in emotional arousal. Eigenvector Centrality did not vary for any nodes in the network as a result of arousal effects.

No measures of Local Assortativity were significant. This is not surprising, given that Global Assortativity was not significantly related to arousal rating.

#### 4. Discussion

The need for inhibition of responses to task-irrelevant emotional challenge involves a restructuring of the functional brain network to increase communication between goal-driven attention-allocation regions and stimulus-driven emotion-processing regions. Accordingly,

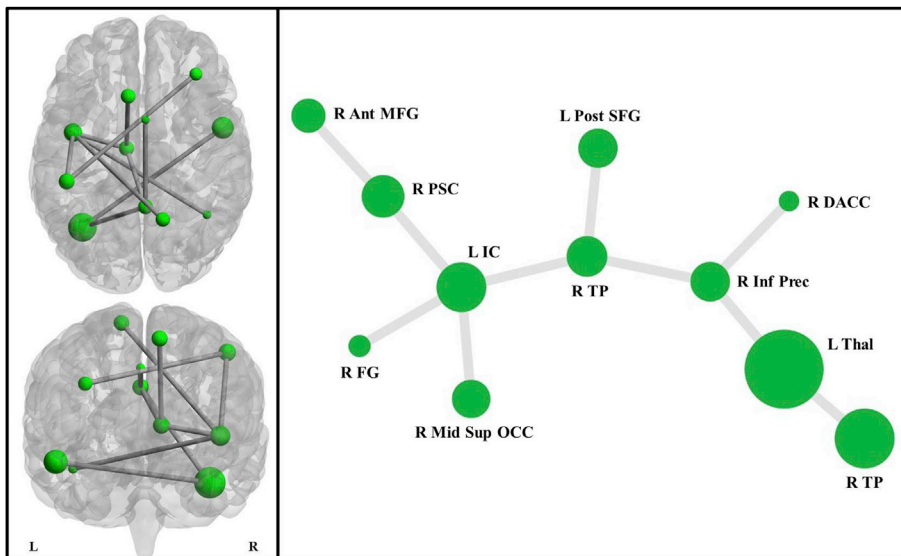


Fig. 3. Second network configuration that increases in strength during negative relative to positive words ( $p = 0.004$ ). Thresholding significant comparisons at  $t = 3.2$  and significant networks at  $p = 0.05$ . Areas included in the network are as follows: right dorsal anterior cingulate, R DACC; right anterior medial frontal gyrus, R Ant MFG; right fusiform gyrus, R FG; right middle superior occipital cortex, R Mid Sup OCC; right primary sensory cortex, R PSC; right temporal pole, R TP; right inferior precuneus, R Inf Prec; left insular cortex, L IC; left thalamus, L Thal; right temporal pole, R TP.

Table 3  
Summary of graph property results.

	IFC	Insula	Thalamus	Precuneus
<i>Valence</i>				
Participation Coefficient	-	-	-	Neg > Pos
<i>Arousal</i>				
Local Efficiency	High > Low	High > Low	High > Low	High > Low
Brokerage	High < Low		High < Low	High < Low
Closeness Centrality	High > Low	High > Low	High > Low	High > Low
Participation Coefficient	High > Low		High > Low	High > Low

Notes: Table shows results of negative vs. positive “valence” and high vs. low “arousal” contrasts for local graph properties, as calculated by GTG toolbox. Directionality of results is indicated by “>” or “<”. All results are significant at the  $p > 0.05$  level, and corrected for multiple comparisons.

present results demonstrate substantial restructuring of brain networks to accomplish emotional inhibition in a manner that is simultaneously more specialized within modules and more efficient in inter-module communication. Emotional inhibition was associated with strengthening of the role of IFG, thalamus, and precuneus as network hubs as well as increased local and global connectivity and efficiency in order to face the increasing demands of the task. Words rated high in emotional arousal (positive + negative vs. neutral) prompted more functional segregation (i.e., more clustering) and higher overall communication efficiency. Additionally, brain regions typically involved in emotion processing were more closely connected to thalamus, which was positioned as a communication hub supporting information transfer.

#### 4.1. Network connections

Using a network wide regression analysis, individual links were tested and network elements were identified that varied as a function of emotion inhibition. Valence analyses revealed two sub-networks wherein connectivity strength varied. One network centered around highly connected prefrontal nodes, with links to temporal, parietal, and hippocampal regions. The second consisted of a highly connected thalamic hub, with links to prefrontal cortex, insula, cingulate, and occipital and temporal cortices. When considered in the context of a literature that commonly links prefrontal cortex and cingulate with cognitive control processes (Hariri et al., 2000; Ochsner and Gross, 2005; Spielberg et al., 2015) and temporo-parietal regions, insula, and hippocampus with emotion salience (Compton et al., 2003; Garcia-Garcia et al., 2016; Sadeh

et al., 2014), these results are in line with the present hypothesis that emotion inhibition is supported by an interaction between two networks: a goal-driven inhibitory control network centered in prefrontal cortex and a stimulus-driven emotion salience network mediated by thalamus. It should be noted that network-based analyses revealed networks that differed as a function of valence, whereas analysis of graph properties (discussed below) evidenced differences as a function of arousal. These differential relationships indicate that diversity in the methods used to examine networks is crucial, as they may detect different nuances.

#### 4.2. Global network properties

Restructuring of the global network in response to high arousal stimuli involved simultaneous increases in clustering of nodes into specialized clusters (*Transitivity*) and in communication efficiency between these clusters (*Global Efficiency*). The EWS task is hypothesized to involve implementation of goal-driven inhibitory control and subsequent down-regulation of stimulus-driven engagement with emotional stimuli. It follows that, in order to inhibit goal-irrelevant, stimulus-driven emotion processing, inhibition-related sub-networks would benefit from first communicating efficiently within these clusters and then increasing goal-driven influence over emotion-related sub-networks (although the present work does not speak to the direction or temporal order of effects). Inhibitory control of emotion likely involves a goal-driven network including prefrontal cortex, which increases the efficiency of communication with a stimulus-driven emotion processing network, portions of which are instantiated in posterior parietal cortex. Therefore, efficient communication between prefrontal-control and emotion-processing networks would serve to direct attention away from task-irrelevant and toward task-relevant features.

#### 4.3. Node properties

To examine the roles of influential nodes in network changes associated with emotion inhibition, the most highly connected nodes in these emergent networks were selected for further analysis. These nodes included left inferior frontal gyrus, left thalamus, left insula, and right precuneus. Results suggest that left inferior frontal gyrus and left thalamus are particularly important hubs supporting inhibitory control of emotional response. Inferior frontal gyrus and thalamus appear to be surrounded by a highly clustered network (*Local Efficiency*) and are closer to all other nodes in the network (*Closeness Centrality*). This pattern of properties indicates that these nodes become nearer to other nodes in

their networks and their networks become more highly clustered as arousal level of stimuli increases. They play an important role in increasing the efficiency of specialized function within their networks and in network-wide information transfer. Further, both nodes demonstrated that, as arousal level of stimuli increase, they become important points of connection between different modules (*Participation Coefficient*). In particular, inferior frontal gyrus and thalamus shift their role in the network, such that overall efficiency is augmented, by increasing their connections to other clusters. As thalamus frequently demonstrates involvement in inhibition by amplifying prefrontal cortex control (Schmitt et al., 2017), and inferior frontal gyrus is commonly associated with goal-driven attentional control, these findings are consistent with present hypotheses suggesting that interplay between these two systems, beyond the action of each system alone, supports performance on the EWS task.

Precuneus also emerged as an important hub supporting inhibition of emotion response. As with inferior frontal gyrus and thalamus, precuneus was associated with increased connectivity in the local network (*Local Efficiency*), shorter connections to all other nodes in the network (*Closeness Centrality*), and a greater role as a point of communication between the hubs of other modules (*Participation Coefficient*) in instances of both negative word valence and high word arousal. Such findings are consistent with Bullmore and Sporns' (2009) characterization of precuneus as a hub of information transfer between parietal and prefrontal regions. They further suggest that, when emotion inhibition demands are high, precuneus is vitally important in the transfer of information between otherwise unconnected modules.

Insula was shown to occupy a more central position as a network hub (*Closeness Centrality*) and to have increased local clustering (*Local Efficiency*) during high-arousal trials. This finding indicates that insula increases its influence over the network and its neighbors exchange information more efficiently during emotion inhibition. Previous work has shown insula to be active during tasks that require response selection and selective attention (Sheu and Courtney, 2016; Modinos et al., 2015), suggesting that it has a role in supporting goal-driven control of attention. It therefore appears that, as emotion challenge increases, insula moves into a more central role to support the goal-driven control and allocation of goal-oriented attention.

#### 4.4. Limitations

Hypotheses predicted that amygdala would emerge as a significant local network hub supporting emotion inhibition performance. Present results using a network-based-statistic approach did not demonstrate an effect of emotion challenge on amygdala's role in the network structure. Reliance on an extended series of emotion words to prompt an emotional response, particularly given that amygdala response tends to habituate, is a potential explanation for the absence of amygdala involvement. Although the valence and arousal ratings of the words used in this study were externally validated (Bradley and Lang, 1998), it is possible that they were not able to elicit a sufficiently strong emotional response to overcome the limited time course and individual variability in amygdala responsiveness to emotion stimuli, as shown in some previous work (e.g., Canli et al., 2001; Sauder et al., 2013).

#### 4.5. Conclusions

Findings from the present study may provide insight into psychological disorders that evidence disturbances in regulation of emotion. For example, depression and anxiety could plausibly be associated with disruptions in these complex, adaptive network dynamics. Previous work has suggested that inhibition plays an important role in any emotion-regulation strategy (e.g., Falquez et al., 2015), and thus deficits in the successful inhibition of emotional responses to stimuli can have a direct impact on a variety of cognitive processes. Individuals with elevated depression and anxiety display a bias toward negative stimuli and

specifically to threat cues (Mathews, & Tata, 1986; Chan and Lovibond, 1996; Levin et al., 2007; Ellenbogen and Schwartzman, 2009; MacLeod et al., 1986), which suggests deficits in the inhibition of response to emotionally salient stimuli. That is, these individuals may be less able to avoid taking notice of, and reacting to, negatively valenced information (consciously or unconsciously), which results in functional impairment. Such a tendency is further manifested in decreases in EWS performance in individuals with elevated symptoms of depression and anxiety (Dai and Feng, 2011; Williams et al., 1996).

Successful emotion inhibition involves goal-directed, selective attention to one aspect of a stimulus while inhibiting a response to the emotional salience of the stimulus. This process appears to rely on complex communication between hubs of emotion salience and inhibitory control sub-networks. The present study replicates previous work demonstrating that inhibitory control was associated with restructuring of the global network to increase specialized processing and overall communication efficiency, in addition to shifting roles of IFS, insula, and dACC (Spielberg et al., 2015). In addition to this replication, the present study adds to our understanding of how networks are dynamically restructured to support inhibition of different categories of information, as inhibition of emotional response appears to be linked to precuneus and thalamic amplification of prefrontal control on posterior parietal and occipital-temporal regions. Future work should explore how the network structures supporting emotion inhibition outlined here are altered in psychopathology.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroimage.2018.10.066>.

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