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Effective Connectivity Between Broca's Area and Amygdala as a Mechanism of Top-Down Control in Worry

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Abstract

Individuals higher in trait worry exhibit increased activation in Broca's area during inhibitory processing tasks. To identify whether such activity represents an adaptive mechanism supporting top-down control, we investigated functional and effective connectivity of Broca's area during a task of inhibitory control. Functional MRI data obtained from 106 participants performing an emotion-word Stroop task were examined using psychophysiological interaction and Granger causality (GC) analyses. Findings revealed greater directed connectivity from Broca's area to amygdala in the presence of emotional distraction. Furthermore, a predictive relationship was observed between worry and the asymmetry in effective connectivity; worriers exhibited greater directed connectivity from Broca's area to amygdala. When performing the task, worriers with greater GC directional asymmetry were more accurate than worriers with less asymmetry. Present findings indicate that individuals with elevated trait worry use a mechanism of top-down control in which communication from Broca's area to amygdala fosters successful compensation for interference effects.

Keywords

fMRI, Granger causality, inhibition, top-down control, worry

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Anxious apprehension, or worry, is largely considered a pattern of repetitive thinking that is often maladaptive and related to negative mood states and disorders such as generalized anxiety disorder (GAD). Although studies have found relationships between anxious apprehension, impaired executive function, and hypoactivation in related brain regions, recent neuroimaging studies indicate that activation in Broca's area is increased in worriers (Engels et al., 2007; Spielberg et al., 2013). The significance of such heightened activity has yet to be specified, including the possibility that increased activation in Broca's area may serve as part of a compensatory mechanism that facilitates executive function and emotion regulation via communication with other brain regions such that worry can actually be adaptive.

Impaired executive function is frequently observed in psychopathology and involves disruptions across multiple cognitive processes, including planning, flexibility, judgment, goal-directed behavior, and inhibitory processing. When anxiety is elevated and sustained, dysfunctional cognitive mechanisms may predispose individuals to the development of clinical symptoms as well as contribute to symptom maintenance. For example, the failure to inhibit negative elaborative processes such as worry, a hallmark symptom of anxiety, may precipitate negative thoughts (De Raedt & Koster, 2010). Strengthened over time, this failure to inhibit may lead to prolonged processing of negative material, which may in turn result in a reduced ability to recover from

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negative mood while also fostering vulnerability to the development and maintenance of psychopathology (Kertz, Belden, Tillman, & Luby, 2016).

Inhibitory processing involves tuning out irrelevant stimuli and/or suppressing automatic or prepotent behavioral responses to stimuli to pursue goal-directed behavior. Anxious individuals frequently show an impaired ability to inhibit distractors, both externally generated (e.g., loud noises) and internally generated (e.g., thoughts), which may interfere with performance on tasks that require the control of attention (Engels et al., 2007; Eysenck, Derakshan, Santos, & Calvo, 2007). For example, anxious individuals generally perform more slowly than control subjects on the color-word Stroop task (Mathews & Macleod, 1985; Mogg, Mathews, & Weinman, 1989), which requires distractor inhibition as individuals are presented with the name of a color printed in a noncongruent color (e.g., "blue" is printed in red) and must inhibit the word meaning to indicate the color of the printing. Top-down control is required to identify the print color, which is less automatic than word reading, making word meaning difficult to suppress (MacLeod, 1992).

Anxiety is also associated with biases toward negative emotional information (Engels et al., 2007; Mogg & Bradley, 2005; Sass et al., 2010, 2014). Relying on a modified version of the Stroop task, the emotion-word Stroop task is a useful tool for assessing attentional bias toward negative stimuli. During the task, positive (pleasant), neutral, and negative (unpleasant) words are presented in different colors. Participants must respond to the color of the word while suppressing the meaning of the word. The task facilitates examining top-down control in the face of emotional distraction, thus tapping into emotion processing and negativity biases as well as general inhibition. Individuals with anxiety disorders typically exhibit greater interference effects than healthy control subjects such that they take longer to name the colors of unpleasant words than neutral words (Mathews & Macleod, 1985; Mogg & Bradley, 2005; Mogg et al., 1989).

A proposed mechanism supporting these interference effects is that longer reaction times during performance of the emotion-word Stroop task reflect the extent to which the emotional meaning of the word captures attentional resources, thus reducing the attention that can be allocated to the task (Mathews, Ridgeway, & Williamson, 1996). That is, emotional stimuli may trigger task-irrelevant cognitive processes that compete for attentional resources. Such a possibility is supported by findings from neuroimaging studies conducted with healthy individuals. Specifically, increased activation in emotion-processing regions may reduce the resources available to the top-down control regions necessary for the task. Previous work found less bilateral frontal activity, particularly in left dorsolateral prefrontal cortex (DLPFC), for unpleasant than for pleasant words using the emotion-word Stroop task (Herrington et al., 2005). Inhibition often involves the frontal brain regions, including DLPFC. In addition to decreased activation in inhibition-processing regions, more activation in amygdala is observed for unpleasant than for neutral stimuli during the emotion-word Stroop task (Han, Lee, Kim, & Kim, 2014). These findings support a mechanistic model of interference characterized by increased activation in emotion-processing regions, such as amygdala, accompanied by decreased activation in regions implicated in successful inhibition, such as DLPFC, in the presence of negative (unpleasant) emotional distractors.

Imaging studies have similarly investigated neural activation during inhibition tasks in individuals with anxiety. Studies report decreased activation in regions implicated in top-down control, including DLPFC and rostral anterior cingulate cortex, in anxious individuals during inhibitory processing (Beaudreau, MacKay-Brandt, & Reynolds, 2013; Engels et al., 2007). However, Engels and colleagues (2007) found that for negative versus neutral words in the emotion-word Stroop task, individuals higher in anxious apprehension demonstrated greater activity in left inferior frontal gyrus (IFG), approximating Broca's area (Brodmann areas 44 and 45).

Broca's area is most commonly implicated in language production, phonological processing, and comprehension (Awh et al., 1996; Zatorre, Meyer, Gjedde, & Evans, 1996). Broca's area has also been implicated in self-referential activities and may reflect the use of inner speech (Morin & Michaud, 2007). Activation of Broca's area in anxious apprehension is in line with the hypothesis that language centers are involved in worry, a largely verbal process supporting repetitive negative thoughts such as "What if the worst happens?" (Hirsch & Mathews, 2012; Nitschke, Heller, & Miller, 2000). The relationship between anxious apprehension and Broca's area in negative versus neutral trials observed by Engels and colleagues (2007) suggests that this region plays a role in inhibitory processing as well.

Worry's association with increased activity in Broca's area and decreased activation in other top-down control regions lends support to the proposal that increased activity in Broca's area limits resource allocation to other brain regions. Consistent with such a possibility, Spielberg and colleagues (2013) found a negative correlation between activity in Broca's area and right superior frontal gyrus (SFG) during an emotion-word Stroop task in individuals higher in anxious apprehension. SFG has been implicated in attentional control, the reappraisal of negative stimuli, and reduction (i.e., "down-regulation") of arousal (Falquez et al., 2014; Hopfinger, Woldorff, Fletcher, & Mangun, 2001; Johnstone, van

Reekum, Urry, Kalin, & Davidson, 2007; Milham, Banich, & Barad, 2003; Ray & Zald, 2012). Thus, engagement in worrying may be associated with increased activation in Broca's area, which in turn contributes to decreased activation in other top-down control regions needed to perform various cognitive functions.

Alternatively, worry's association with increased activity in Broca's area could represent an adaptive compensatory mechanism supporting cognitive function in response to decreased activation in top-down control regions such as SFG. Research has implicated Broca's area in a broad variety of functions, including the implementation of top-down control (Badre & Wagner, 2007; Nelson, Reuter-Lorenz, Sylvester, Jonides, & Smith, 2003). Color-word Stroop studies have sometimes found that Broca's area is recruited during incongruent trials (Carter et al., 2000; January, Trueswell, & Thompson-Schill, 2009; Mead et al., 2002; Milham et al., 2003); these findings implicate the region in resolving conflicting information even during a task in which little syntactic processing is necessary (Novick, Trueswell, & Thompson-Schill, 2010). Therefore, greater activation in Broca's area could compensate for other cognitive impairments associated with psychopathology. The process by which Broca's area supports top-down control may involve communication with a network of other brain regions such that increased activation in Broca's area corresponds to greater activation in other top-down control regions. Alternatively, increased activation in this frontal region could result in a decrease in activation in regions that respond to emotionally salient distraction, thereby facilitating successful inhibition.

The present project sought to identify a neural mechanism of anxious apprehension by which top-down control is fostered by a network of executive function and emotion regulation brain regions in which Broca's area is embedded (Bartholomew, Yee, Heller, Miller, & Spielberg, 2019; Spielberg, Miller, Heller, & Banich, 2015). During an emotion-word Stroop task, changes in functional connectivity between Broca's area and other regions as a function of cognitive demand (greater interference during negative words than neutral words) were examined to identify the network behavior of brain regions implicated in top-down control dysfunction and compensation in anxious apprehension. To better elucidate causal interactions between regions of this network, we also investigated the effective connectivity of Broca's area.

Three main hypotheses were investigated:

Hypothesis 1: Greater connectivity will be observed between Broca's area and other executive function or emotion regulation regions during task blocks involving greater interference effects (e.g., negative > neutral).

Hypothesis 2: Activation in Broca's area will precede (i.e., Granger cause) the activation of other region or regions identified during task blocks with greater interference effects.

Hypothesis 3: Anxious apprehension will moderate Broca's area functional connectivity and/or effective connectivity with other regions during task blocks involving greater interference effects, which may in turn predict task performance.

Method

Participants

Data were obtained from 133 participants as part of a larger project conducted at the University of Illinois at Urbana-Champaign that collected functional MRI (fMRI) data during the emotion-word and color-word Stroop tasks. The current participants represent a superset of those who contributed data to the work of Spielberg and colleagues (2015), which provides details of subject recruitment. The study was approved by the University of Illinois at Urbana-Champaign Institutional Review Board and carried out in accordance with the provisions of the World Medical Association Declaration of Helsinki.

The Penn State Worry Questionnaire (PSWQ) was administered to assess anxious apprehension (Meyer, Miller, Metzger, & Borkovec, 1990). Because of the high comorbidity between anxious apprehension and other dimensional measures of anxiety and depression, the Mood and Anxiety Symptom Questionnaire (MASQ) scales for anxious arousal (MASQAA) and anhedonic depression (MASQAD8; Watson et al., 1995) were administered and used as covariates in some analyses (Miller & Chapman, 2001; Verona & Miller, 2015) to examine the unique influence of anxious apprehension in the context of factors common to these other dimensions of psychopathology. The MASQAD8 refers to an eight-item subscale of the MASQ Anhedonic Depression scale that has been shown to reflect depressed mood (Nitschke, Heller, Imig, McDonald, & Miller, 2001).

Exclusion criteria from fMRI analysis included claustrophobia, left-handedness, prior serious brain injury, abnormal hearing or vision, metal in body, pregnancy, and nonnative English. In addition, participants were excluded if they exhibited movement of 3.3 mm or more relative to the middle volume, 2 mm or more relative to the previous volume, average relative displacement greater than 0.4 mm; task errors of 15% or more; significant signal loss as a result of susceptibility artifact; and/or serious motion-related activation patterns. After all exclusions, 105 participants remained for analysis. Table 1 provides demographics and PSWQ scores.

Table 1. Demographic Information and Questionnaire Scores

Statistic	Mean	Percentage
Age (years)	34.76 (9.1)	
Gender (female/male)	65/41	
Education (years)	17.14 (2.43)	
Race		
White		84
Black		5.7
Asian		4.6
Native American		0.9
Pacific Islander		0.9
Unknown		3.8
Positive-block RT (ms)	713 (108)	
Neutral-block RT (ms)	715 (107)	
Negative-block RT (ms)	727 (108)	
PSWQ	47.33 (13.7)	
MASQAA	22.04 (4.3)	
MASQAD8	15.1 (4.3)	

Note: Values in parentheses are standard deviations. RT = reaction time; PSWQ = Penn State Worry Questionnaire; MASQAA = Mood and Anxiety Symptom Questionnaire–Anxious Arousal; MASQAD8 = eight-item depressed mood subscale of MASQ Anhedonic Depression scale.

Emotion-word Stroop task and acquisition

Task and fMRI acquisition methods followed those outlined in Bartholomew et al. (2019). In brief, the emotion-word Stroop task consisted of blocks of positive (pleasant) or negative (unpleasant) words alternating with blocks of neutral words. Each word was displayed in one of four colors; each color occurred equally often with each word type. Presentation of 16 blocks (4 positive, 8 neutral, 4 negative) of 16 trials (32 s each) yielded 256 trials. Participants received one of eight counterbalanced block orders designed to ensure that emotional and neutral blocks preceded each other equally often.

Words were selected on the basis of established ratings of arousal and valence (Bradley & Lang, 1999). Before the task, participants were instructed to indicate the color of the word presented on the screen by pressing one of four buttons and to ignore word meaning. In addition to the 16 word blocks, fixation blocks (each 32 s in duration) were presented at the beginning, the end, and twice in the middle of the session. There were also several brief rest periods during the task, totaling 100 s of rest.

Before beginning the emotion-word Stroop task, participants performed 64 practice trials. By the end of the practice trials, no participants failed to understand the task instructions or were unable to map colors to buttons. Participants then completed the task during fMRI acquisition. Average reaction times (RTs) were computed for each condition (positive, neutral, and negative), excluding no-response trials.

Data preprocessing

Preprocessing relied on tools in the FSL analysis package (Jenkinson et al., 2012) and AFNI (afni.nimh.nih.gov/). Initial preprocessing consisted of motion correction using six standard motion parameters and field-map correction via FSL and despiking via AFNI. Additional preprocessing, including high-pass temporal filtering, spatial smoothing, and brain extraction, was conducted in FSL FEAT. GNU Parallel was used for the execution of FEAT commands (Tange, 2011).

Determination of Broca's regions of interest

A Broca's area seed region mask was defined anatomically using a probabilistic Juelich histological atlas to include voxels in Brodmann areas 44 and 45 while minimizing white-matter inclusion (Fig. 1a). For reference, the resulting region of interest (ROI) in the present work had a volume of 519 voxels overlapping with the Broca's region in left IFG identified by Engels et al. (2007) previously associated with anxious apprehension (PSWQ scores) in an independent sample. The anatomical Broca's area mask was registered to individual functional space using FSL FLIRT.

fMRI analysis

A generalized form of context-dependent psychophysiological interactions (gPPI) facilitates investigation of brain region interactions in a task-dependent manner (McLaren et al., 2012). gPPI was chosen because it has been shown to improve model fit and task-dependent activity detection over standard PPI (McLaren, Ries, Xu, & Johnson, 2012). Regional functional connectivity with Broca's area, implicated in anxious apprehension, was examined in the emotion-word Stroop data set for differences in activation in negative versus neutral blocks of the task. Although a voxel-wise approach across the whole brain allows for exploration of all regions associated with Broca's area, including those not predicted from hypotheses, multiple-comparisons correction makes it more difficult to find significant clusters of activity. Therefore, using an approach similar to that of Spielberg et al. (2013), connectivity with Broca's area was examined within a specified subset of emotion regulation regions. The mask was anatomically defined using a Juelich histological atlas and included right IFG,

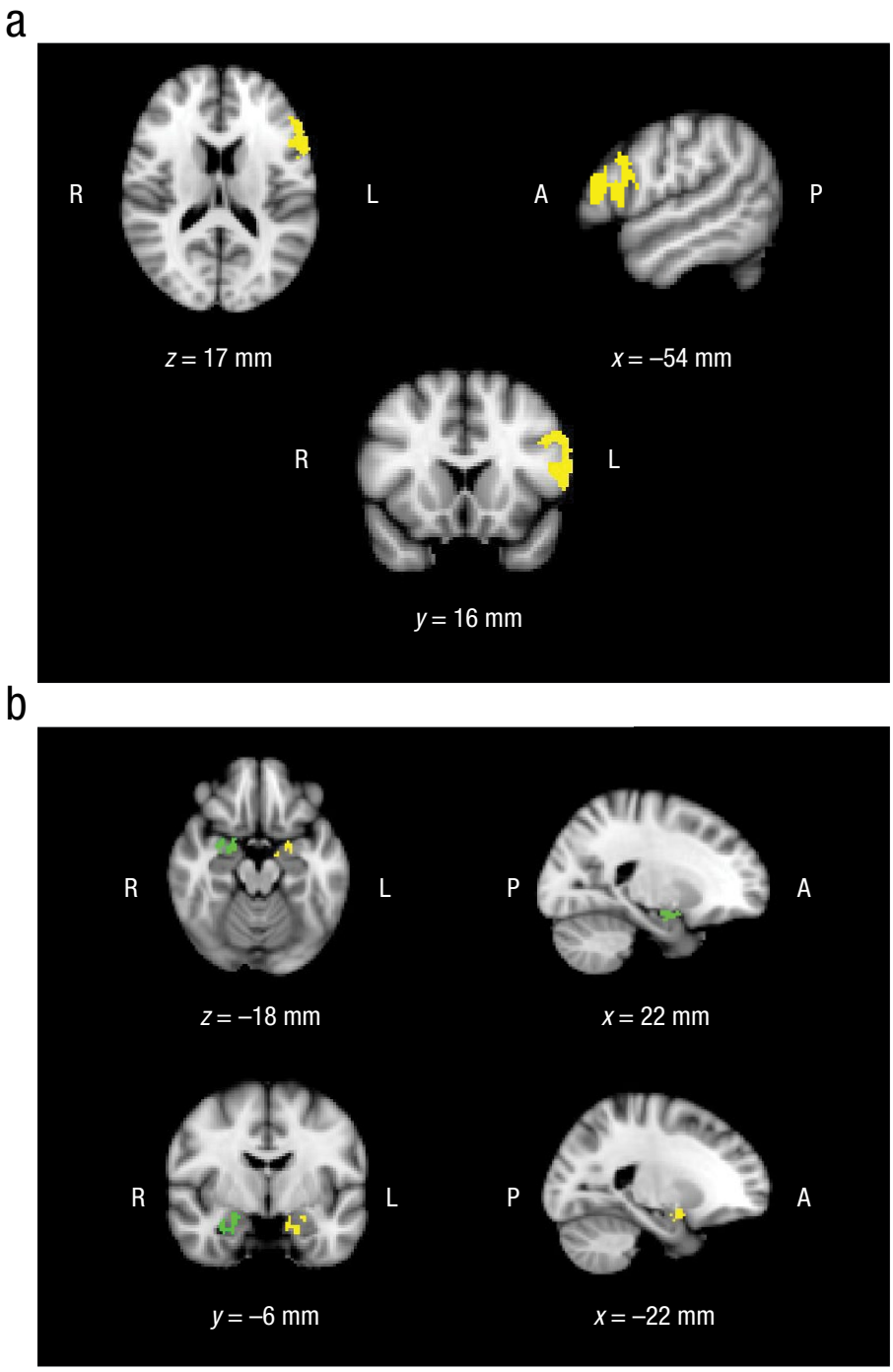

Fig. 1. Broca's area and amygdala regions of interest (ROIs). The Broca's region ROI mask (a; 519 voxels in standard space) was defined anatomically using a probabilistic Juelich histological atlas to include voxels in Brodmann areas 44 and 45 while minimizing white matter inclusion. Amygdala ROIs (b) showing greater connectivity with Broca's area during negative than during neutral trials. A right ROI (90 voxels, center of gravity = [x = 24.5 mm, y = –2.89 mm, z = –18.1 mm], in green) showed connectivity ($p < 0.05$) after permutation testing and correction for the family-wise error rate (FWE) in the generalized psychophysiological interactions (gPPI) analysis. Lateralization analyses with permutation testing were conducted using a left ROI analog developed using the gPPI statistical map (shown in yellow, 77 voxels). Right (R) and left (L) amygdala did not differ in Granger causality connectivity to Broca's area. A = anterior; P = posterior.

bilateral amygdala, anterior cingulate cortex, insula, DLPFC, and medial frontal gyrus. Connectivity analyses were thus confined to these hypothesized ROIs.

The time course of activity was extracted from the Broca's area seed ROI, mean centered, and entered as a physiological regressor in the general linear model analysis in FEAT. The emotion-word Stroop task block types (positive, neutral, negative, and rest) were convolved with a hemodynamic response function and entered as psychological regressors. In addition, nuisance regressors modeling white matter and ventricle signal were included as covariates to account for brain-wide fluctuations (Spielberg et al., 2014). Two interaction terms (Broca's Area Time Course × Negative Blocks = PPI for negative, Broca's Area Time Course × Neutral Blocks = PPI for neutral) were also entered for gPPI. The two interaction terms were then contrasted to examine connectivity differences between these two task conditions.

Second-level analyses were used to examine the main effect of anxious apprehension on the difference in Broca's area connectivity between negative and neutral task conditions. These analyses were conducted using nonparametric permutation testing (5,000 permutations) with FSL Randomise (A. M. Winkler, Ridgway, Webster, Smith, & Nichols, 2014). Threshold-free cluster enhancement (TFCE) was used to find cluster-like structures in the data while fundamentally retaining a voxel-wise image. The FWE rate was controlled for in the TFCE analyses such that only FWE-corrected p values less than .05 were accepted in the resultant p statistical significance images, which illustrate statistically significant clusters of voxels returned by analyses. Resulting cluster locations are given by the voxel coordinates for the center of gravity (COG), which denotes the average of the coordinates weighted by the intensities within the cluster. Voxel-wise analyses were masked to exclude white matter, ventricles, brainstem, and cerebellum.

Beyond identifying the shape of functional neural networks, identification of directional interactions from time-series imaging data can add important functional information. Because the gPPI analyses outlined above examine functional connectivity in an undirected manner, it is not possible to determine directions of causality using this approach. Granger causality (GC) analysis statistically identifies potential causal relationships under the theory that observed time series x causes another time series y if the past of x contains information that helps predict the future of y over and above the information already in the past of y itself (Astolfi et al., 2007; Granger, 1969; Seth, Barrett, & Barnett, 2015). The premise is that a cause cannot come after the effect. The prediction error for the model including x and y is compared with the model excluding x to determine GC of y by x. If the prediction error of y is reduced when the past information of x is taken into account, then x is said to have a Granger causal influence on y.

To examine the effective connectivity of any region or regions identified in the gPPI analysis, we performed a GC analysis to evaluate directionality between activity in Broca's area and identified regions. The methods for GC with fMRI data followed those of Luo, Ge, Grabenhorst, Feng, and Rolls (2013). In brief, mean blood-oxygen-level dependent (BOLD) signals were extracted for each ROI in the gPPI and detrended and zero centered before GC analyses. Formulating the idea of GC in the context of a vector autoregressive model, the GC influence from x to y can be quantified as

$$F_{x\to y} = \log\left[\frac{\det(\sum y)}{\det(\sum yx)}\right],$$

in which a value for $F_{x\to y}$ greater than 0 indicates GC from x to y and a value of 0 indicates otherwise. A log-likelihood ratio test can then be used for causal inference. This statistic is approximately χ^2 distributed with degrees of freedom equal to $2d_xd_y$; d_x and dy are the dimensions of the column vectors representing the time courses of x and y. Because researchers have found that the variation of the BOLD time series across trials increases with the magnitude of the signal, we used an approach that takes into account signal-dependent noise (Luo et al., 2013). To maximize the stability of the autoregressive (AR) model, and because the sampling rate (repetition time) of 2,000 ms in this study, we used a simple first-order (lag-one) model. Examining GC in BOLD time-series data across a lag of one repetition maximizes the temporal resolution in the estimation of neural activity and influence (Hamilton, Chen, Thomason, Schwartz, & Gotlib, 2011). Previous studies using GC in the context of fMRI have similarly used a first-order AR model using various information criteria, and simulation studies have shown that sampling rates of greater than 500 ms demonstrate an optimal order of one (Bressler, Tang, Sylvester, Shulman, & Corbetta, 2008; Roebroeck, Formisano, & Goebel, 2005; Wen, Yao, Liu, & Ding, 2012).

GC analysis was run for each subject within each condition (positive, neutral, and negative trials). Relative frame displacement for each subject was calculated using FSL Motion Outliers and was regressed out of each ROI's time course data before calculating GC to reduce the impact of motion artifact on analyses. Condition blocks (each containing 16 trials) were treated as repeated observations of each condition. Model parameters were estimated for each block, and the model coefficients were then averaged across blocks within a given condition. The log-likelihood function was thus

computed for each condition using the GC model generated by the average of all blocks. Results of the Luo et al. (2013) algorithm showed that all AR models used in the computation of present GC analyses were stable. GC influences were also computed on the time-reversed time series. This strategy accounts for *weak asymmetries* as possible interpretational confounds that could contribute to an apparent dominant directional relationship between two areas (Haufe, Nikulin, Müller, & Nolte, 2013; Popov et al., 2018; I. Winkler, Haufe, Porbadnigk, Müller, & Dähne, 2015).

In brief, in contrast to strong asymmetries, which are caused by actual time-lagged relationships between regions, weak asymmetries are the result of differences in univariate signal properties (e.g., local signal-to-noise ratio). Time reversal of the signals does not affect these univariate signal properties, but it should reverse the dominant direction of interaction. Therefore, if the direction of the GC asymmetry is unchanged after the time reversal, the GC is most likely artifactual, whereas a reversal of the direction of the asymmetry implies a true time-lagged relationship. Original versus time-reversed GC analysis outputs were statistically compared. Because head motion can influence connectivity findings, the relationship between average subject frame displacement and all GC variables was examined (log-likelihood ratios for each direction and asymmetry scores for all conditions). No significant correlations were found (see Table S1 in the Supplemental Material available online).

A Wilcoxon signed-rank test was used to determine which GC direction showed more GC between a pair of ROIs (e.g., the log-likelihood ratio of $x \rightarrow y$ vs. $y \rightarrow x$) within each condition. The difference between GC directionality, the direction and extent of GC asymmetry, was calculated and transformed using Lambert Way to Gaussianize (Goerg, 2015) the data. A Wilcoxon signed-rank test was used to compare conditions on these GC asymmetry scores. To examine whether GC between Broca's area and other ROIs identified in the gPPI was moderated by anxious apprehension, we performed regression analyses to examine PSWQ as a predictor of GC asymmetry. Hierarchical regression analyses also examined the main effects of GC asymmetry and PSWQ and their interaction on accuracy and RT during the emotion-word Stroop task.

Results

Behavioral data

As a manipulation check of interference effects during the emotion-word Stroop task, the effect of condition on RT was examined by entering condition as a within-subjects analysis of variance factor. Results from Mauchly's test of sphericity indicated that the assumption of sphericity was violated, $\chi^2(2) = 9.64$, $p < .01$; therefore, Huynh-Feldt ε correction was used. There was a main effect of condition, $F(2, 188) = 6.66$, $p = .002$, $\varepsilon = .93$, $\eta_p^2 = .066$, in which RT was slower during negative blocks than during positive ($p = .005$) or neutral ($p = .002$) blocks (see Fig. S1 in the Supplemental Material). Although performance deficits on inhibition tasks such as the color-word Stroop task have sometimes been associated with the PSWQ (Silton et al., 2011), PSWQ scores in the present study did not predict RT interference, $R^2 < .001$, $b = -0.10$, $F(1, 92) = 0.13$, $p = .90$, 95% confidence interval (CI) for $b = [-1.74, 1.54]$. In addition, high PSWQ scorers did not have a higher proportion of errors during negative blocks than during neutral or positive blocks, $R^2 = .001$, $F(1, 92) = 0.49$, $p = .81$, 95% CI = [–0.001, 0.001]. Neither anxious arousal nor anhedonic depression scores predicted RT interference or accuracy.

Connectivity with Broca's area ROI for the negative-minus-neutral contrast

In accordance with Hypothesis 1, PPI analysis of the negative-minus-neutral contrast showed activation in Broca's area correlated positively with activation in right amygdala ($p < .05$ after FWE correction, COG = [$x = 24.5$ mm, $y = -2.89$ mm, $z = -18.1$ mm]; see Fig. 1b).

To specify the functional connection between Broca's area and right amygdala, we used GC analyses to examine the directionality of the relationship. Because there was no a priori expectation of a lateralized relationship between Broca's area and right amygdala, lateralization effects were also examined for all of the following analyses using a left hemisphere analog of the right amygdala ROI. The left amygdala ROI was defined as the cluster of voxels showing the greatest effect from the initial gPPI (z statistic > 1.75) constrained to the left amygdala as defined by the Juelich atlas (Fig. 1b). Paired-samples permutation testing (10,000 permutations) revealed no significant differences between the GC analyses with right amygdala, outlined below, and those conducted with the left amygdala analog; this finding suggests that all observed effects reflect relationships with bilateral amygdala.

Hypothesis 2 was that activation in Broca's area would precede activation in right amygdala during negative trials. Figure 2a shows stronger GC for the negative-word condition in the Broca's-area-to-amygdala direction ($M = 2.24$, $SD = 1.85$) than in the converse direction ($M = 1.56$, $SD = 1.48$), $p < .001$, 95% CI for the difference between means = [0.32, 1.03]; this finding suggests a top-down influence of Broca's area over amygdala. Furthermore, this GC asymmetry was

greater during negative trials than during positive trials ($M = 0.15$, $SD = 1.86$), $p < .001$, 95% CI for the difference between means = [0.47, 1.39], or neutral trials ($M = –0.10$, $SD = 1.62$), $p < .001$, 95% CI for the difference between means = [0.72, 1.62] (Fig. 2b). Reversal of the original time-series data reversed the direction of this time-lagged relationship in negative trials; this finding indicated that the observed GC during negative trials in the original data reflects unbiased, directed effective influence of Broca's area on amygdala beyond mere correlation (see Fig. S2 in the Supplemental Material).

Hypothesis 3 was that anxious apprehension would moderate functional and/or effective connectivity of Broca's area. PSWQ scores did not significantly moderate the functional connectivity between Broca's area and the right amygdala ROI identified in the gPPI analysis, $b = 0.001$, 95% CI for $b = [–0.0004, 0.003]$, $p = .11$ (see Fig. S3 in the Supplemental Material). No other regions were identified in which PSWQ scores moderated changes in connectivity with Broca's area during the task. In contrast, PSWQ scores moderated effective connectivity between Broca's area and right amygdala. Hierarchical regression evaluated the impact of PSWQ scores and possible confounds with anxious arousal and anhedonic depression. PSWQ, MASQAA, and MASQAD8 together contributed 15% of the variance in GC asymmetry, $F(3, 100) = 6.88$, $p < .001$. MASQAA and MASQAD8 added first did not predict this asymmetry, $R^2 = –.013$, $F(2, 101) = 0.36$, $p = .70$; MASQAA: $t = 0.81$, $p = .42$, MASQAD8: $t = –0.063$, $p = .95$, whereas PSWQ added third contributed unique variance, $\Delta R^2 = .16$, $b = 0.054$, $t = 4.45$, $p < .001$, 95% CI for $b = [0.03, 0.078]$. Figure 3a shows that, indeed, higher PSWQ scores were associated with greater GC asymmetry ($r = .41$, $p < .001$).

Neither GC asymmetry nor PSWQ predicted accuracy during negative trials. A trending GC Asymmetry × PSWQ interaction indicated that greater GC asymmetry favoring Broca's area to amygdala was associated with higher accuracy for individuals scoring higher on the PSWQ, $F(1, 91) = 3.92$, $p = .052$, $\Delta R^2 = .037$ (Fig. 3b). No main or interaction effects were found for PSWQ and GC asymmetry in predicting RT during negative trials. The GC Asymmetry × PSWQ interaction was such that greater GC asymmetry favoring Broca's area to amygdala was associated with faster RTs for individuals scoring higher on the PSWQ, $F(1, 92) = 4.18$, $p = .035$, $\Delta R^2 = .048$ (Fig. 3c). These two findings indicate that higher asymmetry prompted better performance for participants higher in worry.

Discussion

This project evaluated the effective connectivity between Broca's area and amygdala during a top-down control task. Negative-word trials prompted higher functional connectivity between Broca's area and amygdala, which confirmed the first hypothesis. Although a right amygdala ROI was identified by this analysis, permutation testing revealed that left and right amygdala did not differ in connectivity or causality with Broca's area. Results indicate that Broca's area interacts more with amygdala when a task requires greater top-down control, such as in the presence of emotional distractors.

GC analysis was used to identify causal influences between these regions. In support of the second hypothesis, effective connectivity from Broca's area to amygdala was higher during negative trials. Activity in Broca's area preceding activity in amygdala is evidence of top-down control in which Broca's area suppresses amygdala to decrease interference and promote cognitive performance despite the greater challenge of negative trials.

Although anxious apprehension did not moderate overall functional connectivity between Broca's area and amygdala, it predicted the degree of GC directional asymmetry, in support of the third hypothesis. In particular, individuals with a greater tendency to worry exhibited greater directed connectivity from Broca's area to amygdala during negative-word trials. Note that this top-down control was apparently adaptive: Worriers with greater GC asymmetry from Broca's area to amygdala demonstrated better performance than worriers with less asymmetry.

Present findings lend support to the proposal that Broca's area is involved in various cognitive and top-down control processes (Badre & Wagner, 2007; Carter et al., 2000; January et al., 2009; Mead et al., 2002; Milham et al., 2003; Nelson et al., 2003). Evidence of increased functional coupling of Broca's area and amygdala during negative trials of the emotion-word Stroop task supports studies implicating the importance of frontal-limbic connectivity during tasks involving emotion down-regulation. Increased functional coupling of inferior frontal cortex and amygdala has been observed during the processing of emotional distractors. More specifically, left-lateralized inferior frontal activation has been shown to be associated with successful emotion inhibition (Dolcos, Kragel, Wang, & McCarthy, 2006). The present results build on this frontal-limbic emotion regulation mechanism by providing evidence for an effective relationship wherein activation in Broca's area precedes activation in amygdala during inhibition of processing of negative emotional material. When there is a greater need for inhibitory control, such as during negative trials of the emotion Stroop task, Broca's area can suppress amygdala to decrease interference and promote cognitive function.

Although imaging and other studies have provided diverse evidence for the involvement of frontal regions and associated modulation of amygdala activation during

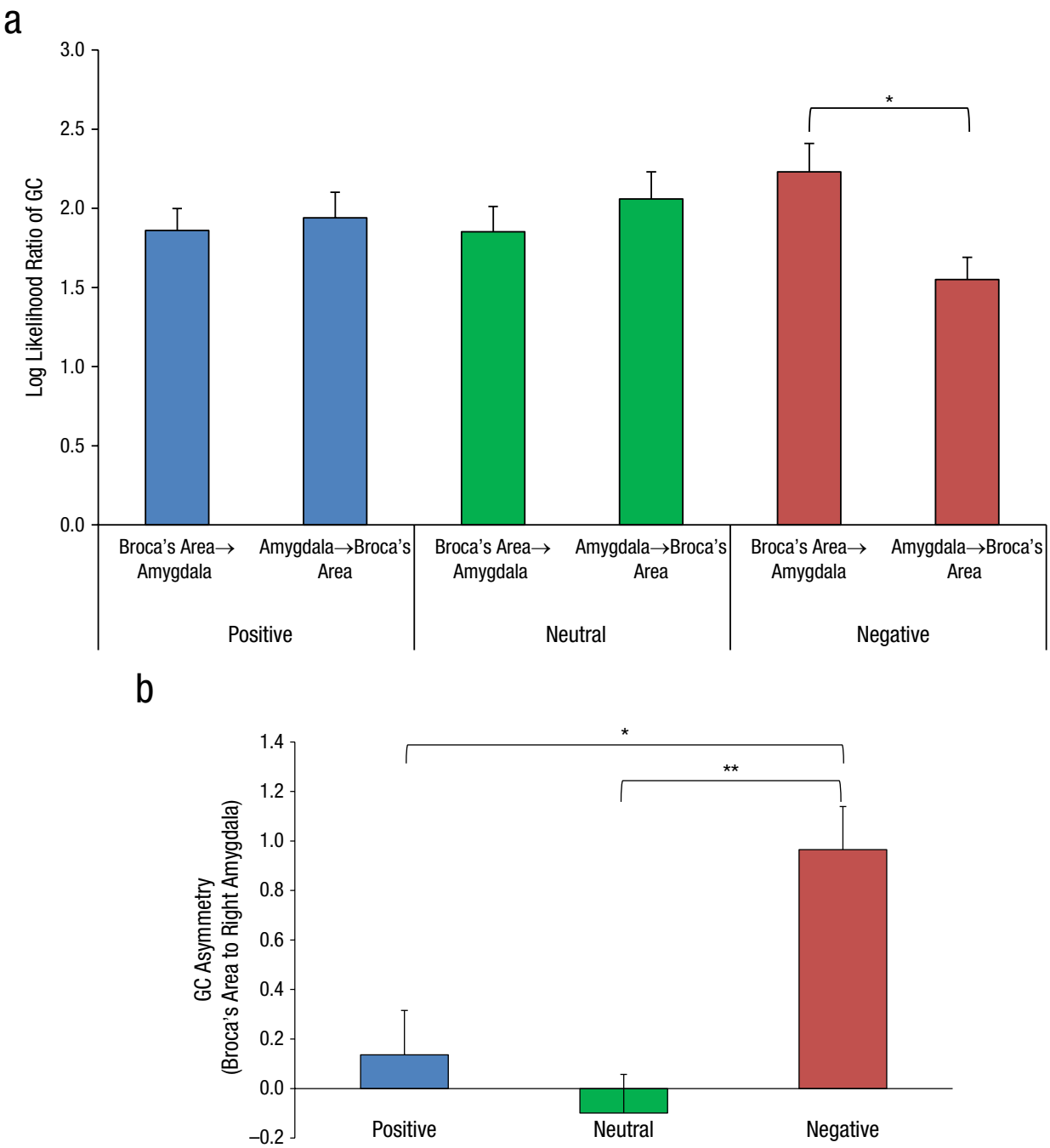

Fig. 2. Granger causality (GC) asymmetry between Broca's area and right amygdala. Greater GC was found from Broca's area to right amygdala (a) than from right amygdala to Broca's area in the negative-word condition. No significant GC asymmetry between Broca's area and right amygdala was found for positive or neutral trials. Mean Gaussianized GC asymmetry scores (b) were calculated for positive-, neutral-, and negative-word conditions. Mean asymmetry is greatest for negative words. Error bars denote +1 *SE*. Asterisks represent significant differences between conditions (*$p < .05$; **$p < .001$).

tasks requiring emotion regulation, present results indicate that Broca's area plays a key role in this regulation of anxiety. Greater Broca's area to amygdala effective connectivity corresponds to more successful inhibition of emotional distractors to support goal-directed behavior, suggestive of a successful compensatory mechanism. Engagement in worrying may prime Broca's area in a way that supports this increased effective connectivity, as a means of acute top-down control. The extent to which anxious individuals exhibit this directed connectivity predicts their ability to effectively exert top-down control in the face of negative emotional content.

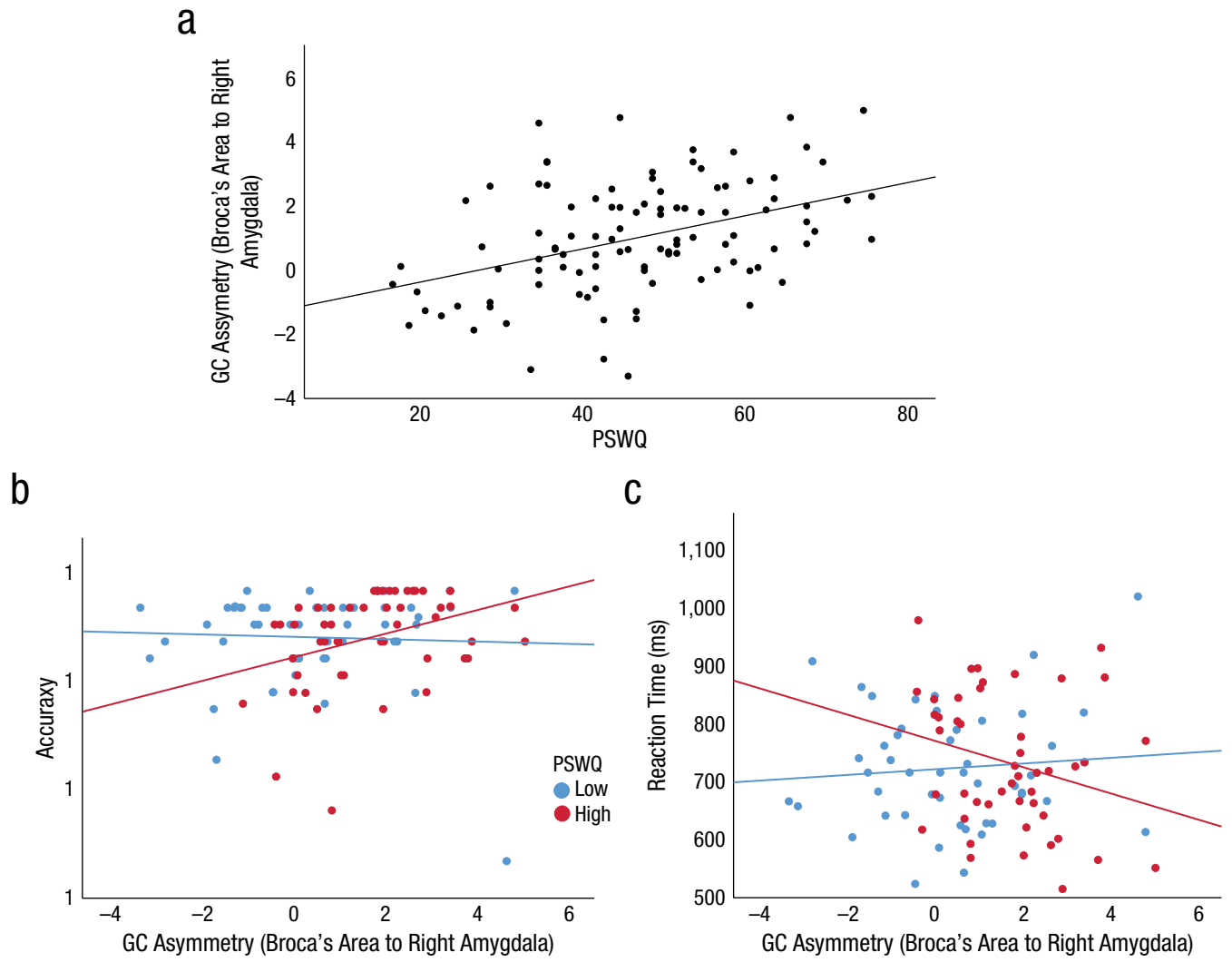

Fig. 3. Granger causality (GC) asymmetry and anxious apprehension. Scatterplot (a; with best-fitting regression line) shows the association between Penn State Worry Questionnaire (PSWQ) scores and GC asymmetry (from Broca's area to right amygdala). Scatterplot (b; with best-fitting regression lines) shows the association between task accuracy and GC asymmetry, separately for low and high scorers on the PSWQ. Scatterplot (c; with best-fitting regression lines) shows the association between task reaction times and GC asymmetry, separately for low and high scorers on the PSWQ.

The inability to effectively regulate negative emotion represents a vulnerability to the development of psychopathology (Banks, Eddy, Angstadt, Nathan, & Luan Phan, 2007; Gross, 2002). Present findings suggest that effective connectivity from Broca's area to amygdala represents a successful mechanism of top-down emotion regulation in worriers. This performance facilitation supports the proposal of the developers of the PSWQ that worry can have some adaptive functions (Borkovec, 1994; Borkovec, Alcaine, & Behar, 2004). The cognitive avoidance model of worry suggests that worry can serve to dampen somatic arousal associated with anxiety and preclude emotional processing (Newman & Llera, 2011; Stapinski, Abbott, & Rapee, 2010). Effective connectivity from Broca's area to amygdala may represent a mechanism supporting this emotional avoidance in worry such that top-down control from Broca's area disrupts emotional processing and facilitates performance on the emotion-word Stroop task. The greater this top-down control is, the less worriers experienced interference by emotionally salient distraction.

Although anxiety is commonly thought of as maladaptive, characterized by emotion-congruent biases in attention resulting in greater attention to negative material (Yiend, 2010), worriers who are effectively able to exert this top-down control may be better able to regulate emotion in a variety of contexts. In this manner, greater connectivity in this direction may serve to counteract the

inhibitory dysfunction commonly associated with various types of psychopathology. However, although in the present study worriers displaying greater directed connectivity from Broca's area to amygdala were better able to inhibit negative emotional content, the associated avoidance of emotional processing may predict other negative outcomes such as behavioral avoidance and reduced social or occupational function. Future research should examine factors and individual differences that determine whether this mechanism serves as an adaptive or maladaptive strategy of avoidance. Ottaviani and colleagues (2014) suggested, for example, that the cognitive avoidance model wherein worry is adaptive applies to healthy control subjects but not to pathological worriers. Research is needed to clarify the benefits and disadvantages associated with this neural mechanism of top-down control and elucidate factors that may predict or strengthen this mechanism and its effects on functional outcomes.

Continued exploration of the neural circuitry involved in anxious apprehension and inhibitory processing may provide a better understanding of anxiety. In addition, it was posited that not only worry but also a more general, "perseverative-iterative" style, a tendency to dwell on a topic of concern, is associated with activation in left IFG–Broca's area (Berenbaum, 2010). Expanding research to examine Broca's area role in various contributors to worry, such as catastrophizing or ruminative thinking, may elucidate mechanisms involved in multiple forms of psychopathology. Further examination of neural networks involved in inhibitory processing may also contribute to improving interventions either generally or targeted for particular individuals given the connectivity patterns they demonstrate (Craver & Bechtel, 2007; Miller, 2010). Present findings have implications for mindfulness practices, which often work to disrupt worry by focusing attention elsewhere (e.g., to the individual's breathing or proprioception). As a healthier alternative to worry, mindfulness training was shown to increase activation in left IFG during the anticipation of negative stimuli, which may facilitate emotion regulation (Lutz et al., 2013). The Broca's area–amygdala circuit may also represent a target for psychotherapy adaptations, cognitive remediation training, and pharmaceutical or transcranial stimulation interventions (Caulfield, Tyler Ketchabaw, Pascual-Leone, Press, & Stern, 2016). Prefrontal cortex stimulation in individuals with trait anxiety was recently found to reduce amygdala threat reactivity and improve performance on an attentional task (Ironside et al., 2017). Given the present findings, Broca's area–left IFG may represent a similarly effective target of intervention, particularly in individuals presenting with higher levels of anxious apprehension or GAD.

In the present project, we conducted an analysis of effective connectivity using GC analysis, which to date is rarely applied to fMRI time series (Luo et al., 2013; Wen et al., 2012). The use of GC with fMRI data is nevertheless largely untried and potentially controversial, and limitations to its use should be considered in the interpretation of our findings. Previous work noted the limitations of the GC approach in modeling only linear, stationary relationships (Seth et al., 2015; Stokes & Purdon, 2017). In addition, much of the concern in using GC with fMRI data is related to the indirect relationship between the BOLD signal and the neural activity of interest (Ramsey et al., 2010). In particular, the low temporal sampling rate is a concern given that the time scale of much neuronal activity is on the order of milliseconds, whereas the typical TR of fMRI data is on the order of seconds. Therefore, interpretation of GC is limited in fMRI data in terms of temporal resolution. The scope of GC analysis was limited here to using the past activity of one ROI to predict the future of the other ROI at a lag of 1 TR = 2,000 ms. Although the length of the TR makes it impossible to capture changes in neural activity faster than the hemodynamic response, analysis using a lag greater than one TR would be even further removed from modeling the relevant neural activity, as discussed above in the Method section. Examination of electroencephalographic (EEG) data during the same task would provide improved ability to detect GC at a variety of lags (cf. our use of EEG in a color-word Stroop task; Popov et al., 2018). Use of EEG would also serve to avoid concerns that latency in the hemodynamic response function may differ across brain regions.

In summary, in this project, we evaluated functional and effective connectivity with Broca's area during an emotion-word Stroop task as a function of anxious apprehension. GC analysis provided evidence of apparent causal influences between these regions, specifically greater directed connectivity from Broca's area to amygdala when greater top-down control was useful to pursue goal-directed behavior in the presence of emotional distractors. Anxious apprehension predicted the extent of effective connectivity asymmetry between these regions such that worriers exhibited greater effective connectivity from Broca's area to amygdala. This work synthesizes research supporting the role of left IFG–Broca's area in emotion regulation, related to frontal-limbic connectivity, and the conceptualization of worry as inner speech associated with altered Broca's area function. Present findings suggest that individuals with a proclivity for worry may use a mechanism of top-down control in which communication from Broca's area to amygdala represents successful compensation of interference effects. Researchers should continue to

examine the nature of this mechanism. Increased understanding of effective connectivity between Broca's area–left IFG and amygdala in the context of negative emotionality and attention tasks could serve to elucidate mechanisms of both healthy performance and therapeutic effects across a variety of tasks and treatments.

Action Editor

Erin B. Tone served as action editor for this article.

Author Contributions

A. Guha developed the study concept, performed the analyses, and wrote the manuscript. J. M. Spielberg contributed to the preprocessing of neuroimaging data. J. M. Spielberg and J. Lake contributed to generalized form of context-dependent psychophysiological interactions analytic techniques. T. Popov contributed to the Granger causality analytic methods. G. A. Miller and W. Heller conceived and designed the study for which these data were originally collected. G. A. Miller and C. M. Yee provided oversight and helped shape the analysis and the manuscript. All of the authors discussed the results, contributed to the writing of the final manuscript, and approved the final manuscript for submission.

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Declaration of Conflicting Interests

The author(s) declared that there were no conflicts of interest with respect to the authorship or the publication of this article.

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Supplemental Material

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References

Astolfi, L., De Vico Fallani, F., Cincotti, F., Mattia, D., Marciani, M. G., Bufalari, S., . . . Babiloni, F. (2007). Imaging functional brain connectivity patterns from high-resolution EEG and fMRI via graph theory. *Psychophysiology*, *44*, 880–893. doi:10.1111/j.1469-8986.2007.00556.x

Awh, E., Jonides, J., Smith, E. E., Schumacher, E. H., Koeppe, R. A., & Katz, S. (1996). Dissociation of storage and rehearsal in verbal working memory: Evidence from positron emission tomography. *Psychological Science*, *7*, 25–31. doi:10.1111/j.1467-9280.1996.tb00662.x

Badre, D., & Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia*, *45*, 2883–2901. doi:10.1016/j.neuropsychologia.2007.06.015

Banks, S. J., Eddy, K. T., Angstadt, M., Nathan, P. J., & Phan, K. L. (2007). Amygdala–frontal connectivity during emotion regulation. *Social Cognitive and Affective Neuroscience*, *2*, 303–312. doi:10.1093/scan/nsm029

Bartholomew, M. E., Yee, C. M., Heller, W., Miller, G. A., & Spielberg, J. M. (2019). Reconfiguration of brain networks supporting inhibition of emotional challenge. *NeuroImage*, *186*, 350–357. doi:S105381191832038X

Beaudreau, S. A., MacKay-Brandt, A., & Reynolds, J. (2013). Application of a cognitive neuroscience perspective of cognitive control to late-life anxiety. *Journal of Anxiety Disorders*, *27*, 559–566. doi:10.1016/j.janxdis.2013.03.006

Berenbaum, H. (2010). An initiation–termination two-phase model of worrying. *Clinical Psychology Review*, *30*, 962–975.

Borkovec, T., Alcaine, O., & Behar, E. (2004). Avoidance theory of worry and generalized anxiety disorder. In R. G. Heimberg, C. L. Turk, & D. S. Mennin (Eds.), *Generalized anxiety disorder: Advances in research and practice* (pp. 77–108). New York, NY: Guilford Press.

Borkovec, T. D. (1994). The nature, functions, and origins of worry. In G. C. L. Davey & F. Tallis (Eds.), *Worrying: Perspectives on theory, assessment and treatment* (pp. 5–33). Oxford, England: John Wiley & Sons.

Bradley, M. M., & Lang, P. J. (1999). *Affective norms for English words (ANEW): Instruction manual and affective ratings*. Technical report C-1, the Center for Research in Psychophysiology, University of Florida.

Bressler, S. L., Tang, W., Sylvester, C. M., Shulman, G. L., & Corbetta, M. (2008). Top-down control of human visual cortex by frontal and parietal cortex in anticipatory visual spatial attention. *The Journal of Neuroscience*, *28*, 10056–10061. doi:10.1523/JNEUROSCI.1776-08.2008

Carter, C., Macdonald, A., Botvinick, M., Ross, L. L., Stenger, V., Noll, D., & Cohen, J. D. (2000). Parsing executive processes: Strategic vs. evaluative functions of the anterior cingulate cortex. *Proceedings of the National Academy of Sciences, USA*, *97*, 1944–1948. doi:10.1073/pnas.97.4.1944

Caulfield, K. A., Tyler Ketchabaw, W., Pascual-Leone, A., Press, D. Z., & Stern, A. P. (2016). Reductions in depression and anxiety measures are correlated in patients receiving transcranial magnetic stimulation. *Brain Stimulation*, *9*(5), Article e9. doi:10.1016/j.brs.2016.06.028

Craver, C. F., & Bechtel, W. (2007). Top-down causation without top-down causes. *Biology & Philosophy*, *22*, 547–563. doi:10.1007/s10539-006-9028-8

De Raedt, R., & Koster, E. (2010). Understanding vulnerability for depression from a cognitive neuroscience perspective: A reappraisal of attentional factors and a new conceptual framework. *Cognitive, Affective, & Behavioral Neuroscience*, *10*, 50–70. doi:10.3758/CABN.10.1.50

Dolcos, F., Kragel, P., Wang, L., & McCarthy, G. (2006). Role of the inferior frontal cortex in coping with distracting emotions. *NeuroReport*, *17*, 1591–1594. doi:10.1097/01.wnr.0000236860.24081.be

Engels, A. S., Heller, W., Mohanty, A., Herrington, J. D., Banich, M. T., Webb, A. G., & Miller, G. A. (2007). Specificity of regional brain activity in anxiety types during emotion processing. *Psychophysiology*, *44*, 352–363. doi:10.1111/j.1469-8986.2007.00518.x

Eysenck, M. W., Derakshan, N., Santos, R., & Calvo, M. G. (2007). Anxiety and cognitive performance: Attentional control theory. *Emotion*, *7*, 336–353. doi:10.1037/1528-3542.7.2.336

Falquez, R., Couto, B., Ibanez, A., Freitag, M. T., Berger, M., Arens, E. A., . . . Barnow, S. (2014). Detaching from the negative by reappraisal: The role of right superior frontal gyrus (BA9/32). *Frontiers in Behavioral Neuroscience*, *8*, Article 165. doi:10.3389/fnbeh.2014.00165

Goerg, G. M. (2015). The Lambert way to Gaussianize heavy-tailed data with the inverse of Tukey's h transformation as a special case. *Scientific World Journal*, 2015, Article 909231. doi:10.1155/2015/909231

Granger, C. W. J. (1969). Investigating causal relations by econometric models and cross-spectral methods. *Econometrica*, *37*, 424–438. doi:10.2307/1912791

Gross, J. J. (2002). Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology*, *39*, 281–291. doi:10.1017/S0048577201393198

Hamilton, J. P., Chen, G., Thomason, M. E., Schwartz, M. E., & Gotlib, I. H. (2011). Investigating neural primacy in Major Depressive Disorder: Multivariate Granger causality analysis of resting-state fMRI time-series data. *Molecular Psychiatry*, *16*, 763–772. doi:10.1038/mp.2010.46

Han, H. J., Lee, K., Kim, H. T., & Kim, H. (2014). Distinctive amygdala subregions involved in emotion-modulated Stroop interference. *Social Cognitive and Affective Neuroscience*, *9*, 689–698. doi:10.1093/scan/nst021

Haufe, S., Nikulin, V. V., Müller, K. R., & Nolte, G. (2013). A critical assessment of connectivity measures for EEG data: A simulation study. *NeuroImage*, *64*, 120–133. doi:10.1016/j.neuroimage.2012.09.036

Herrington, J. D., Mohanty, A., Koven, N. S., Fisher, J. E., Stewart, J. L., Banich, M. T., . . . Heller, W. (2005). Emotion-modulated performance and activity in left dorsolateral prefrontal cortex. *Emotion*, *5*, 200–207. doi:10.1037/1528-3542.5.2.200

Hirsch, C. R., & Mathews, A. (2012). A cognitive model of pathological worry. *Behaviour Research and Therapy*, *50*, 636–646. doi:10.1016/j.brat.2012.06.007

Hopfinger, J. B., Woldorff, M. G., Fletcher, E. M., & Mangun, G. R. (2001). Dissociating top-down attentional control from selective perception and action. *Neuropsychologia*, *39*, 1277–1291. doi:10.1016/S0028-3932(01)00117-8

Ironside, M., Browning, M., Ansari, T., Harvey, C., Sekyi-Djan, M., Bishop, S., . . . Shea, J. (2017). Prefrontal cortex regulates amygdala response to threat in trait anxiety. *BioRxiv*, Article 215699. doi:10.1101/215699

January, D., Trueswell, J. C., & Thompson-Schill, S. L. (2009). Co-localization of Stroop and syntactic ambiguity resolution in Broca's area: Implications for the neural basis of sentence processing. *Journal of Cognitive Neuroscience*, *21*, 2434–2444. doi:10.1162/jocn.2008.21179

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). Fsl. *NeuroImage*, *62*, 782–790.

Johnstone, T., van Reekum, C. M., Urry, H. L., Kalin, N. H., & Davidson, R. J. (2007). Failure to regulate: Counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. *The Journal of Neuroscience*, *27*, 8877–8884. doi:10.1523/JNEUROSCI.2063-07.2007

Kertz, S. J., Belden, A. C., Tillman, R., & Luby, J. (2016). Cognitive control deficits in shifting and inhibition in preschool age children are associated with increased depression and anxiety over 7.5 years of development. *Journal of Abnormal Child Psychology*, *44*, 1185–1196. doi:10.1007/s10802-015-0101-0

Luo, Q., Ge, T., Grabenhorst, F., Feng, J., & Rolls, E. T. (2013). Attention-dependent modulation of cortical taste circuits revealed by Granger causality with signal-dependent noise. *PLOS Computational Biology*, *9*(10), Article e1003265. doi:10.1371/journal.pcbi.1003265

Lutz, J., Herwig, U., Opialla, S., Hittmeyer, A., Jäncke, L., Rufer, M., . . . Brühl, A. B. (2013). Mindfulness and emotion regulation—An fMRI study. *Social Cognitive and Affective Neuroscience*, *9*, 776–785. doi:10.1093/scan/nst043

MacLeod, C. M. (1992). The Stroop task: The "gold standard" of attentional measures. *Journal of Experimental Psychology: General*, *121*, 12–14. doi:10.1037/0096-3445.121.1.12

Mathews, A., & Macleod, C. (1985). Selective cues processing in anxiety of threat. *Behaviour Research and Therapy*, *23*, 563–569. doi:10.1016/0005-7967(90)90160-K

Mathews, A., Ridgeway, V., & Williamson, D. A. (1996). Evidence for attention to threatening stimuli in depression. *Behaviour Research and Therapy*, *34*, 695–705. doi:10.1016/0005-7967(96)00046-0

McLaren, D. G., Ries, M. L., Xu, G., & Johnson, S. C. (2012). A generalized form of context-dependent psychophysiological interactions (gPPI): A comparison to standard approaches. *NeuroImage*, *61*, 1277–1286. doi:10.1016/j.neuroimage.2012.03.068

Mead, L. A., Mayer, A. R., Bobholz, J. A., Woodley, S. J., Cunningham, J. M., Hammeke, T. A., & Rao, S. M. (2002). Neural basis of the Stroop interference task: Response competition or selective attention? *Journal of the International Neuropsychological Society*, *8*, 735–742. doi:10.1017/S1355617702860015

Meyer, T. J., Miller, M. L., Metzger, R. L., & Borkovec, T. D. (1990). Development and validation of the Penn State Worry Questionnaire. *Behaviour Research and Therapy*, *28*, 487–495. doi:10.1016/0005-7967(90)90135-6

Milham, M. P., Banich, M. T., & Barad, V. (2003). Competition for priority in processing increases prefrontal cortex's involvement in top-down control: An event-related fMRI study of the Stroop task. *Cognitive Brain Research*, *17*, 212–222. doi:10.1016/S0926-6410(03)00108-3

Miller, G.A., & Chapman, J.P. (2001). Misunderstanding analysis of covariance. *Journal of Abnormal Psychology*, *110*, 40–48.

Miller, G. A. (2010). Mistreating psychology in the decades of the brain. *Perspectives on Psychological Science*, *5*, 716–743. doi:10.1177/1745691610388774

Mogg, K., & Bradley, B. P. (2005). Attentional bias in generalized anxiety disorder versus depressive disorder. *Cognitive therapy and research*, *29*, 29–45. doi:10.1007/s10608-005-1646-y

Mogg, K., Mathews, A., & Weinman, J. (1989). Selective processing of threat cues in anxiety states: A replication. *Behaviour Research and Therapy*, *27*, 317–323. doi:10.1016/0005-7967(89)90001-6

Morin, A., & Michaud, J. (2007). Self-awareness and the left inferior frontal gyrus: Inner speech use during self-related processing. *Brain Research Bulletin*, *74*, 387–396. doi:10.1016/j.brainresbull.2007.06.013

Nelson, J. K., Reuter-Lorenz, P. A., Sylvester, C. Y., Jonides, J., & Smith, E. E. (2003). Dissociable neural mechanisms underlying response-based and familiarity-based conflict in working memory. *Proceedings of the National Academy of Sciences, USA*, *100*, 11171–11175. doi:10.1073/pnas.1334125100

Newman, M. G., & Llera, S. J. (2011). A novel theory of experiential avoidance in generalized anxiety disorder: A review and synthesis of research supporting a contrast avoidance model of worry. *Clinical Psychology Review*, *31*, 371–382.

Nitschke, J. B., Heller, W., Imig, J. C., McDonald, R. P., & Miller, G. A. (2001). Distinguishing dimensions of anxiety and depression. *Cognitive Therapy and Research*, *25*, 1–22. doi:10.1023/A:1026485530405

Nitschke, J. B., Heller, W., & Miller, G. A. (2000). Anxiety, stress, and cortical brain function. In J. C. Borod (Ed.), *Series in affective science: The neuropsychology of emotion* (pp. 298–319). New York, NY: Oxford University Press.

Novick, J. M., Trueswell, J. C., & Thompson-Schill, S. L. (2010). Broca's area and language processing: Evidence for the cognitive control connection. *Language and Linguistics Compass*, *4*, 906–924. doi:10.1111/j.1749-818X.2010.00244.x

Ottaviani, C., Borlimi, R., Brighetti, G., Caselli, G., Favaretto, E., Giardini, I., . . . Sassaroli, S. (2014). Worry as an adaptive avoidance strategy in healthy controls but not in pathological worriers. *International Journal of Psychophysiology*, *93*, 349–355.

Popov, T., Westner, B. U., Silton, R. L., Sass, S. M., Spielberg, J. M., Rockstroh, B., . . . Miller, G. A. (2018). Time course of brain network reconfiguration supporting inhibitory control. *The Journal of Neuroscience*, *38*, 4348–4356. doi:10.1523/JNEUROSCI.2639-17.2018

Ramsey, J. D., Hanson, S. J., Hanson, C., Halchenko, Y. O., Poldrack, R. A., & Glymour, C. (2010). Six problems for causal inference from fMRI. *NeuroImage*, *49*, 1545–1558.

Ray, R. D., & Zald, D. H. (2012). Anatomical insights into the interaction of emotion and cognition in the prefrontal cortex. *Neuroscience & Biobehavioral Reviews*, *36*, 479–501. doi:10.1016/j.neubiorev.2011.08.005

Roebroeck, A., Formisano, E., & Goebel, R. (2005). Mapping directed influence over the brain using Granger causality and fMRI. *NeuroImage*, *25*, 230–242. doi:10.1016/j.neuroimage.2004.11.017.

Sass, S. M., Heller, W., Fisher, J. E., Silton, R. L., Stewart, J. L., Crocker, L. D., . . . Miller, G. A. Electrophysiological evidence of the time course of attentional bias in non-patients reporting symptoms of depression with and without co-occurring anxiety. *Frontiers in Psychology*, *5*, Article 301. doi:10.3389/fpsyg.2014.00301

Sass, S. M., Heller, W., Stewart, J. L., Silton, R. L., Edgar, J. C., Fisher, J. E., & Miller, G. A. (2010). Time course of attentional bias in anxiety: Emotion and gender specificity. *Psychophysiology*, *47*, 247–259. doi:10.1111/j.1469-8986.2009.00926.x

Seth, A. K., Barrett, A. B., & Barnett, L. (2015). Granger causality analysis in neuroscience and neuroimaging. *The Journal of Neuroscience*, *35*, 3293–7. doi:10.1523/JNEUROSCI.4399-14.2015

Silton, R. L., Heller, W., Engels, A. S., Towers, D. N., Spielberg, J. M., Edgar, J. C., . . . Miller, G. A. (2011). Depression and anxious apprehension distinguish frontocingulate cortical activity during top-down attentional control. *Journal of Abnormal Psychology*, *120*, 272–85. doi:10.1037/a0023204

Spielberg, J. M., De Leon, A. A., Bredemeier, K., Heller, W., Engels, A. S., Warren, S. L., . . . Miller, G. A. (2013). Anxiety type modulates immediate versus delayed engagement of attention-related brain regions. *Brain and Behavior*, *3*, 532–551. doi:10.1002/brb3.157

Spielberg, J. M., Miller, G. A., Heller, W., & Banich, M. T. (2015). Flexible brain network reconfiguration supporting inhibitory control. *Proceedings of the National Academy of Sciences, USA*, *112*, 10020–10025. doi:10.1073/pnas.1500048112

Spielberg, J. M., Miller, G. A., Warren, S. L., Sutton, B. P., Banich, M., & Heller, W. (2014). Transdiagnostic dimensions of anxiety and depression moderate motivation-related brain networks during goal maintenance. *Depression and Anxiety*, *31*, 805–813. doi:10.1002/da.22271

Stapinski, L. A., Abbott, M. J., & Rapee, R. M. (2010). Evaluating the cognitive avoidance model of generalised anxiety disorder: Impact of worry on threat appraisal, perceived control and anxious arousal. *Behaviour Research and Therapy*, *48*, 1032–1040.

Stokes, P. A., & Purdon, P. L. (2017). A study of problems encountered in Granger causality analysis from a neuroscience perspective. *Proceedings of the National Academy of Sciences, USA*, *114*, E7063–E7072.

Tange, O. (2011). GNU Parallel: The command-line power tool. *Login: The USENIX Magazine*, *36*, 42–47. doi:10.5281/zenodo.16303

Verona, E., & Miller, G.A. (2015). Analysis of covariance. In R. L. Cautin & S. O. Lilienfeld (Eds.), *The encyclopedia of clinical psychology* (pp. 136-142). New York, NY: Wiley.

Watson, D., Clark, L. A., Weber, K., Assenheimer, J. S., et al. (1995). Testing a tripartite model: II. Exploring

the symptom structure of anxiety and depression in student, adult, and patient samples. *Journal of Abnormal Psychology*, *104*, 15–25. doi:10.1037/0021-843X.104.1.15

Wen, X., Yao, L., Liu, Y., & Ding, M. (2012). Causal interactions in attention networks predict behavioral performance. *The Journal of Neuroscience*, *32*, 1284–1292. doi:10.1523/JNEUROSCI.2817-11.2012

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *NeuroImage*, *92*, 381–397. doi:10.1016/j.neuroimage.2014.01.060

Winkler, I., Haufe, S., Porbadnigk, A. K., Müller, K. R., & Dähne, S. (2015). Identifying Granger causal relationships between neural power dynamics and variables of interest. *NeuroImage*, *111*, 489–504. doi:10.1016/j.neuroimage.2014.12.059

Yiend, J. (2010). The effects of emotion on attention: A review of attentional processing of emotional information. *Cognition and Emotion*, *24*, 3–47.

Zatorre, R. J., Meyer, E., Gjedde, A., & Evans, A. C. (1996). PET studies of phonetic processing of speech: Review, replication, and reanalysis. *Cerebral Cortex*, *6*, 21–30. doi:10.1093/cercor/6.1.21