

Error-Specific Cognitive Control Alterations in Generalized Anxiety Disorder

James F. Cavanagh, Alexandria Meyer, and Greg Hajcak

ABSTRACT

BACKGROUND: Trait anxiety is reliably associated with enhanced neural responses following errors: meta-analyses have described how the electrophysiological response to errors known as error-related negativity (ERN) is increased in anxious individuals, particularly in relation to worry. ERN has been related to a broader class of control signals, particularly via a common theta band denominator, but it is unknown whether worry relates to these alternative medial frontal metrics. Moreover, it is unclear if increased ERN in anxiety relates to altered cognitive control.

METHODS: We examined electroencephalogram activities in subjects with generalized anxiety disorder (GAD) ($n = 39$) and control subjects ($n = 52$) during an executive control task. We leveraged a previously defined theta band network to examine if an altered control signal in GAD underlies a differential implementation of cognitive control.

RESULTS: GAD and control groups were reliably dissociated by error-related and conflict-related neural activity in both time and frequency (i.e., theta band) domains. Moreover, we demonstrated that ERN, error-related theta power, and the single trial correlation between theta and response time were unique predictors of GAD status. Overall, we were able to account for nearly a quarter of the group variance and successfully classify GAD from control participants with two-thirds accuracy.

CONCLUSIONS: Collectively, these findings suggest that multiple neural metrics of error processing may uniquely distinguish individuals with clinical anxiety from healthy individuals and that mechanisms of control also differ in GAD; finally, these error-related neural measures have the potential to be sensitive and specific biosignatures of anxiety.

Keywords: Anxiety, Classification, Cognitive control, ERN, N2, Theta

<http://dx.doi.org/10.1016/j.bpsc.2017.01.004>

A wealth of studies has identified a reliable correlation between trait anxiety and an enhanced electrophysiological response to motor errors of commission (1,2). A growing literature has interpreted this error-driven electrophysiological response, known as error-related negativity (ERN), in terms of a generic, primitive, domain-general process that signals the need for increased cognitive control (3–5). This view of ERN is consistent with the notion that errors are inherently aversive and motivate behavioral adaptation (6,7).

Two recent meta-analyses have highlighted the specificity and sensitivity of this relationship. Moser *et al.* (1) detailed how the relationship between anxiety and ERN amplitude appears to be specific to apprehension or worry. Cavanagh and Shackman (7) described a related generality, where dispositional anxiety is also associated with larger signals of conflict or punishment. Errors, conflict, and punishments all share common psychological significance of inherent aversion and signal the increased need for control. The electrophysiological markers of these events also share a common denominator of midfrontal theta band activities, which have been advanced as a candidate mechanism for the implementation of cognitive control (8).

Despite the potential functional similarity of errors (i.e., ERN) and conflict (i.e., N2) and apparent similarity of these event-related potentials (ERPs) in terms of common theta

band activities, few studies have systematically evaluated these neural metrics within the same sample. For instance, no study has simultaneously examined ERN and N2—as well as their theta band representations—in relation to clinical anxiety. In this report, we aimed to address the outstanding question of whether clinical anxiety is characterized by increased error-related theta as well as time-domain and frequency-domain representations of conflict processing—or, alternatively, if clinical anxiety is better characterized by increased ERN alone.

Furthermore, we assessed whether larger theta band-related activities have functional consequences and reflect enhanced cognitive control in individuals with clinical anxiety. Prior work has revealed that after an error, midfrontal cortex is transiently theta band phase synchronous with other brain regions involved in the exertion of control [see (8) for a review of 11 replications of this finding]. Moreover, ERN or theta power amplitude is predictive of the degree of post-error response time (RT) slowing after an error [again significant in a meta-analysis (7)]. These two findings offer established methods to examine the interactive neural systems involved in the realization and communication of cognitive control.

For the first time, we tested whether anxious individuals have enhanced control (i.e., larger single-trial brain-behavior

relationship, more phase synchrony) following potentiated neural signals to errors and conflict. We tested these relationships in a relatively pure sample of individuals with clinical anxiety with high dispositional worry who met diagnostic criteria for generalized anxiety disorder (GAD). We not only provide novel evidence for altered features of cognitive control in GAD, but we also demonstrate that the use of theta band network activities contributes to better classification of subjects with GAD versus control subjects than ERPs alone.

METHODS AND MATERIALS

The current study combined participants from two separate previously published studies that examined ERN in relation to GAD (9,10). The current study focused on 39 participants with a diagnosis of GAD (but not comorbid depression) and 52 individuals with no current DSM-IV diagnosis (healthy control subjects). All diagnoses were made using DSM-IV (11). Self-reported symptoms of anxiety and depression were gathered from most participants using the Mood and Anxiety Symptom Questionnaire (MASQ) (12). The MASQ is a 62-item self-report measure of mood and anxiety symptoms. In one of the articles that previously reported on these data, we found that ERN was related to the General Distress Anxiety symptoms subscales (9); however, no relationship between ERN and MASQ subscales was found in the other study (10).

Table 1 shows demographic and questionnaire information. Between groups, age did not significantly differ for either study or the combined total ($t_s < 1.18$), but MASQ scores differed in all comparisons for each study and for the combined total ($t_s > 2.8$). Within each group, the age range of the studies differed, but the symptomatology did not (GAD group, $t_s < 1$; control group, $t_s < 1.77$). [For additional information on recruiting and patient information, see (9,10).]

An arrow version of the flanker task was administered using Presentation software (Neurobehavioral Systems, Inc., Berkeley, CA). On each trial, five horizontally aligned arrowheads were presented. Half of all trials were compatible (e.g., “< < < < <”), and half were incompatible (e.g., “< < > < <”). The order of compatible and incompatible trials was random. All stimuli were presented for 200 ms followed by an intertrial interval that varied randomly from 2300 to 2800 ms. Participants performed a practice block containing 30 trials. The

actual task consisted of 11 blocks of 30 trials (330 trials total) with each block initiated by the participant.

Continuous electroencephalogram (EEG) recordings were collected using an elastic cap and the BioSemi ActiveTwo system (BioSemi B.V., Amsterdam, Netherlands) at 1024 Hz with a 208-Hz low-pass filter. Based on the 10/20 system, 33 electrode sites were used as well as two electrodes on the right and left mastoids. The electro-oculogram generated from eye movements and eye blinks was recorded using four facial electrodes: horizontal eye movements were measured via two electrodes located approximately 1 cm outside the outer edge of the right and left eyes. Offline, eye blinks were removed using independent component analyses (13). Data were then referenced to the average of the left and right mastoids.

Only participants with six or more errors were included in EEG analyses (14–16); one participant from the control group and two from the GAD group were removed. All data were analyzed at the FCz electrode. ERPs were low-pass filtered at 20 Hz and baseline corrected from –500 to –300 ms (9,10). N2 was quantified as the mean voltage \pm 25 ms approximately 275 ms after stimulus onset; ERN/correct response negativity was quantified as the mean voltage \pm 25 ms approximately 50 ms after error/correct trials.

The analytic procedure leveraged two existing approaches that previously examined the role of theta power in behavioral control (17,18). To control for trial count and motor activity differences between correct and error epochs, a subset of correct trial EEG epochs was selected based on the closest RT match to each error trial (17). Conflict-related analyses were taken from subsets of correct trials where congruent and incongruent trials each followed congruent trials, capitalizing on the Gratton effect, where congruent-congruent trial sequences maximally differ from congruent-incongruent trial sequences (18).

All time-frequency and statistical methods used wavelet convolution (for time-frequency plots) and band-pass filter–Hilbert (for frequency-specific analyses) with parameters identical to previously published work (19). Wavelet power was normalized by conversion to a decibel scale, allowing a direct comparison of effects across frequency bands. Time-frequency plots were cluster thresholded based on 200 permutations of group label using two-sided $p < .05$ criteria. For discriminant analyses, stimulus-locked theta (4–8 Hz) power was taken from a 300- to 500-ms window; response-

Table 1. Demographic and Questionnaire Information for Subjects With Generalized Anxiety Disorder and Control Subjects in Each Study

	Generalized Anxiety Disorder			Control		
	Total	Study 1	Study 2	Total	Study 1	Study 2
<i>N</i>	39	15	24	52	21	31
Female	95%	87%	100%	85%	62%	100%
Age, Years, Mean (SD)	26.56 (10.07)	31.67 (13.30)	23.38 (5.69)	25.29 (8.46)	30.62 (9.76)	21.68 (4.97)
Has MASQ	82%	93%	75%	92%	100%	87%
MASQ Scores, Mean (SD)						
MASQ Distress: Depression	27.47 (10.52)	26.71 (6.40)	28.06 (13.03)	18.21 (6.70)	17.38 (7.24)	18.85 (6.30)
MASQ Distress: Anxiety	25.69 (7.43)	25.50 (5.52)	25.83 (8.80)	15.13 (4.26)	13.95 (3.98)	16.04 (4.31)
MASQ Anhedonic Depression	63.91 (14.21)	63.64 (10.00)	64.11 (17.07)	49.90 (12.27)	46.43 (13.80)	52.59 (10.41)
MASQ Anxious Arousal	28.47 (8.00)	26.86 (5.46)	29.72 (9.49)	20.15 (4.29)	19.10 (3.32)	20.93 (4.80)

MASQ, Mood and Anxiety Symptom Questionnaire.

Errors Classify Generalized Anxiety Disorder

locked theta power was extracted from 100 to 250 ms postresponse.

All connectivity analyses follow the approach used in Figure 4 in Cavanagh *et al.* (17). This approach investigated the three-way interplay between 1) midfrontal theta power to errors, 2) midfrontal-lateral theta phase synchrony following errors, and 3) post-error RT slowing. In the current study, we investigated if these phenomena and the relationships between each differ between GAD and control groups.

These single-trial analyses used a Laplacian transform of the data, which is necessary to minimize volume conduction before connectivity analyses (20). The vertices of the analytic triangle were based on single-trial estimates of 1) theta power following errors; 2) intersite phase clustering over trials (ISPC-trials), which was calculated as the consistency in phase angle difference between FCz and separate dorsolateral electrodes (i.e., F3/4) across error trials; and 3) post-error RT slowing, calculated as the post-error minus error RT difference, although other methods of quantification [i.e., post-error RT alone, post-error minus preceding correct trial (21)] yielded nearly identical findings to those reported here. Not all single-trial analyses could be performed on ISPC-trial, as it is a trial average; thus, analysis of trial-to-trial synchrony required the computation of ISPC over time (ISPC-time), which is the consistency in phase angle difference over time (within any single trial). Thus, ISPC-time can be computed on single trials, but it was constrained to a scalar value representing the average of phase angle differences over a period between 0 and 200 ms (17). Vertex connections were quantified as the following: 1 and 2) a bar graph of average Spearman correlations between theta power and ISPC-time in the time period of 0 to 200 ms; 1 and 3) a time course of Spearman correlations between instantaneous theta power and RT slowing; and 2 and 3) a bar graph of average Spearman correlations between ISPC-time (0–200 ms) and RT slowing.

Classification used the least absolute shrinkage and selection operator (LASSO) algorithm (22), a penalized logistic regression method, as well as a linear support vector machine (SVM). The average of 5000 iterations of control and GAD samples were reported from three cross-validation methods: 5-times, 10-times, and leave-one-out. The LASSO penalty shrinks regression coefficients in the training stage (setting many to zero) based on tuning parameters, highlighting the smallest subset of important and reliable predictors. LASSO yields multiple solutions to the training set, given different tuning parameters that constrain the sparseness of the logistic regression. To select among these parameters, the regularization weight with the best accuracy on a validation set was selected; to diminish capitalization on chance, the predictive accuracy of these LASSO weights were assessed on a unique test set (23). Average accuracies on this unbiased second validation set are reported here. The SVM does not select the most influential features, so it did not require a separate validation set, and all accuracies were reported based on the sole test set.

RESULTS

Behavior

Analyses of behavioral data were performed separately from trial-count matching and selection procedures implemented for EEG

analysis. Subjects with GAD and control subjects did not differ in the number of errors committed (GAD group, median errors = 29, interquartile range = 14; control group, median errors = 33, interquartile range = 26; $t_{86} = 1.22, p = .23$) or RT for any trial type ($t_s < 1.6$) (Figure 1). When quantifying post-error slowing as the RT difference between post-error and the preceding error trials, the groups were still highly similar in measures of central tendency ($t_{86} = 1.21, p = .23$) and dispersion (SDs $t_{86} < 1$). Thus, collectively, the two groups did not significantly differ on any behavioral measure.

ERPs and Time Frequency

Figure 2 displays the ERPs for each group. An analysis of variance revealed a significant group (GAD, control) \times type (conflict, congruent) \times event (stimulus, response) three-way interaction ($F_{1,86} = 4.5, p = .037$) and a significant group \times type two-way interaction ($F_{1,86} = 9.370, p = .002$). Simple effects contrasts revealed that conflict N2 ($t_{86} = 2.22, p = .03$) and ERN ($t_{86} = 2.95, p = .004$) were significantly different between groups, whereas congruent N2 ($t = 1.53, p = .13$) and correct response negativity ($t = 0.25, p = .80$) were not. Figure 3 displays the group differences in the time-frequency spectrographs of total power (phase-locked, such as an ERP, as well as non-phase-locked) in these conditions. These findings reveal enhanced power in the theta band (4–8 Hz) for subjects with GAD versus control subjects in both conflict and error conditions. There were no significant group differences in intertrial phase consistency in the theta band for any of these conditions, suggesting that theta power is specifically

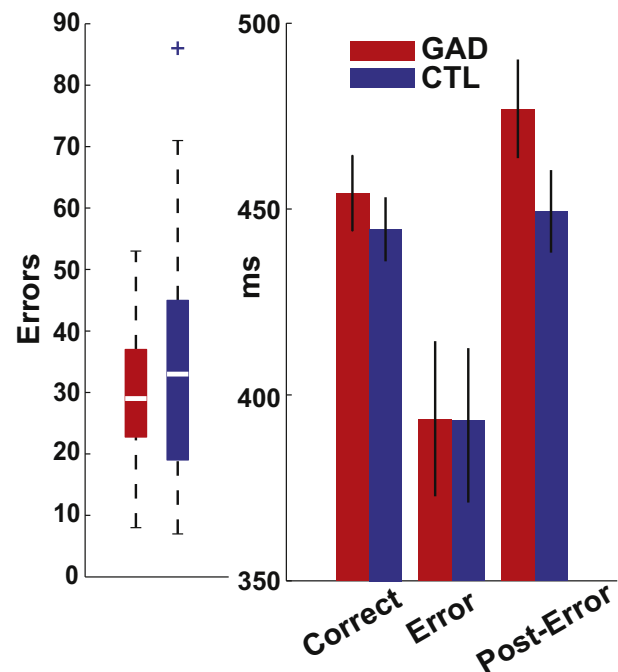


Figure 1. Performance in the generalized anxiety disorder (GAD) and control (CTL) groups on the flanker task. Error rate was similar between groups. While both groups displayed faster errors and slower post-error trials, there were no significant differences in response times.

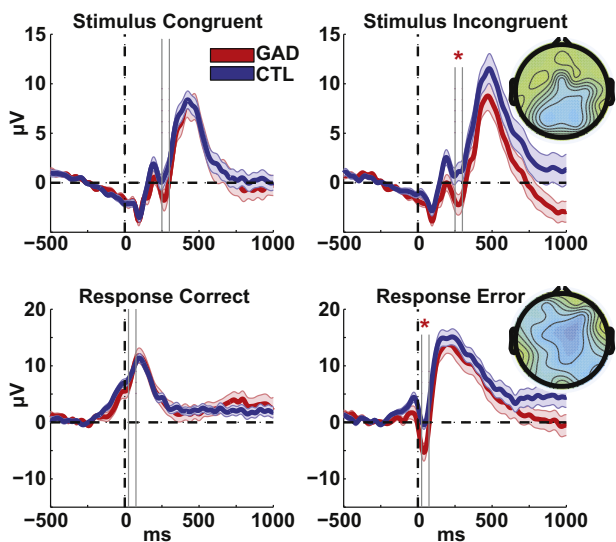


Figure 2. Event-related potentials. As in prior work, the generalized anxiety disorder (GAD) group had larger conflict (N2) and error-related (error-related negativity) voltage enhancements. Topographical maps are condition differences in the significant time windows, $\pm 10 \mu\text{V}$. Asterisks indicate $p < .05$ between groups. CTL, control.

altered in GAD. This is an important distinction, as it has recently been argued that non-phase-locked power is more sensitive to conflict (24).

Common and Unique Variance

Table 2 presents correlations between GAD status and all error-related and conflict-related neural measures. As expected from Figures 1 and 2, GAD was associated with larger ERN and N2 as well as increased error-related and conflict-related theta. ERN and N2 were uniquely related, whereas error-related and conflict-related theta were uniquely related. To examine whether these measures predicted unique variance in GAD status, a stepwise regression analysis predicted GAD status using these four variables. ERN was the best single predictor of GAD, accounting for 9% of the variance in group status ($F_{1,86} = 8.69, p < .01$); theta power predicted another 9% ($F_{1,85} = 9.17, p < .01$); incremental $F_{1,85} = 8.86, p < .01$); and conflict-related variables failed to account for a significant increment (at the .05 level). This finding suggests that error trial activities effectively capture the discriminant variance of interest. While Figure 3 shows a delta band difference for stimulus-locked activities, delta band activities did not contribute any meaningful variance to the analyses in this report.¹ We next addressed what these error-specific theta differences may mean for cognitive control in GAD.

¹When stimulus-locked delta power is included in the stepwise-regression models, it does not add any unique variance. When network-level analyses were run with delta band phenomena, none of the connectivity effects were significant as main effects or as moderated by the GAD group.

Table 2. Correlations Between Clinical Group (GAD), ERN, N2, Error-Related Theta, and Conflict-Related Theta

	GAD	ERN	Conflict N2	Error Theta
ERN	-.30 ^a			
Conflict N2	-.23 ^b	.55 ^a		
Error Theta	.30 ^a	-.03	.005	
Conflict Theta	.27 ^b	-.02	.002	.85 ^a

All values are two-tailed, all EEG data are linked-mastoids referenced. For ERPs, greater negative values indicate enhanced activity; for power, the relationship is isomorphic. Pearson correlations are presented; those between continuous variables are product-moment correlations, while the correlations with the categorical GAD variable are point-biserial correlations. $N = 88$.

EEG, electroencephalogram; ERN, error-related negativity; ERPs, event-related potentials; GAD, generalized anxiety disorder.

^a $p < .01$.

^b $p < .05$.

Mechanisms of Control

To test whether larger error signals in GAD are associated with altered cognitive control, an a priori analytic suite was leveraged (17). We described above how groups did not differ in post-error behavioral adjustment at the group level, but they did differ in the degree of ERN amplitude and midfrontal theta power to errors. Figure 4 details Laplacian-transformed theta-band network findings involved in communicating the error signal to influence post-error behavioral adjustment. This

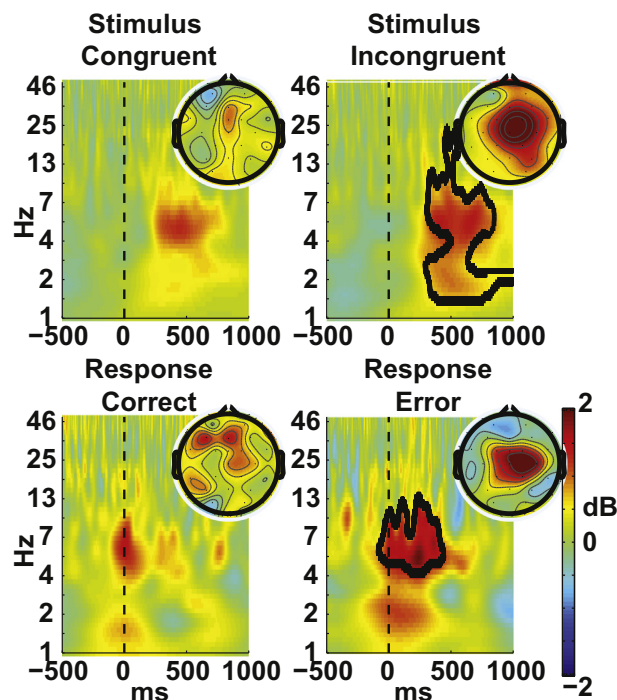


Figure 3. Time-frequency plots of the generalized anxiety disorder group minus control group. Topographical maps are generalized anxiety disorder group minus control group from 300 to 500 ms for stimuli and 100 to 250 ms for responses (stimulus congruent/response correct: $\pm 5 \text{ dB}$, stimulus incongruent/response error: $\pm 10 \text{ dB}$). Outlines show statistically significant differences between groups $p < .05$, permutation corrected.

Errors Classify Generalized Anxiety Disorder

figure is arranged as a triangle, with vertices representing brain or behavioral differences and connections between vertices representing the interplay between midfrontal theta power to errors, midfrontal-lateral theta phase synchrony following errors, and post-error RT slowing. The interplay between vertices is taken as evidence of theta band-mediated networks for behavioral adaptation, providing a test of the hypothesis that larger error signals in GAD represent alterations in the implementation of cognitive control.

Figure 4A details the recently described finding of enhanced midfrontal theta power to errors. When the groups were collapsed, there was no main effect for the predictive power of error-related midfrontal theta power on post-error behavioral adjustment ($t < 1$); however, this was due to a significant difference in the directionality of this relationship between groups ($t_{86} = 2.70, p = .008$), with each group having near-significant one-sample relationships (control group, frontal theta predicted RT slowing [$t_{36} = 1.91, p = .06$]; GAD

group, frontal theta predicted RT speeding [$t_{50} = -1.80, p = .08$]) (Figure 4B). This finding in the control group thus replicates prior findings that frontal theta power predicts RT slowing after an error (8,17). However, this relationship is reversed in GAD—providing the first evidence that enhanced frontal theta in GAD relates to an alteration in cognitive control.

The second facet of this control network was the theta band phase-synchronous relationship between medial and lateral frontal sites following errors (17). Single-trial right-lateralized phase connectivity over this time range (ISPC-time) significantly correlated with the degree of midfrontal theta power ($t_{87} = 18.15, p < .001$), but this measure did not differ between groups ($p = .10$) (Figure 4C). There was a significant increase in mediolateral phase connectivity (ISPC-trial) immediately after errors in both right and left lateral sides ($t_{87} > 5.55, p_s < .001$) (Figure 4D inset). The GAD group had enhanced phase connectivity compared with the control group, but this was only on the right side and only in the error

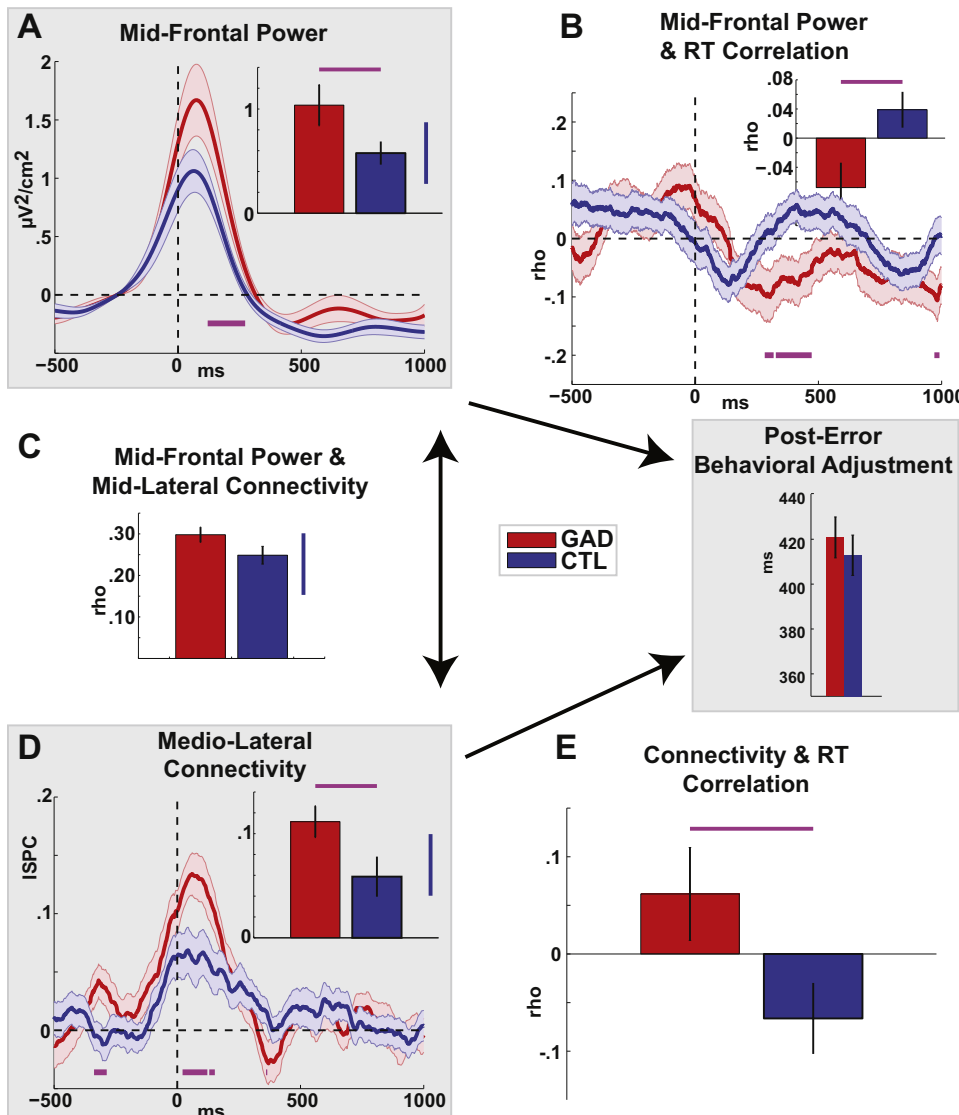


Figure 4. A theta band network for behavioral adaptation following errors differed between the generalized anxiety disorder (GAD) group and control (CTL) group. Horizontal magenta lines indicate group differences ($p < .05$). Vertical blue lines indicate main effects (i.e., >0), $p < .05$. (A) Theta power was larger in the GAD group following errors (inset shows average of 100–250 ms). (B) Increased theta predicted response time (RT) slowing in the CTL group but RT speeding in the GAD group (inset shows average of 300–500 ms). (C) Power correlated with phase synchrony between medial and lateral sites after errors. (D) Right-sided mediolateral phase synchrony was increased after errors (inset shows average of 0–200 ms), and it was larger in the GAD group. (E) Increased synchrony predicted RT speeding in the CTL group but RT slowing in the GAD group. ISPC, intersite phase clustering.

minus correct difference (0–200 ms: $t_{86} = 2.20$, $p = .03$) (Figure 4D).

Finally, when collapsed across groups, there was no significant main effect of right lateralized ISPC-time predicting post-error behavioral adjustment ($t < 1$), but again this was due to directional differences in the groups ($t_{86} = 2.14$, $p = .04$), where the groups had an inverted dissociation as observed in the midfrontal power findings (control group, theta synchrony predicted RT speeding [$t_{36} = -1.27$, $p = .21$]; GAD group, theta synchrony predicted RT slowing [$t_{50} = 1.80$, $p = .08$]) (Figure 4E). This collection of phase synchrony findings complements the interpretation of altered cognitive control in GAD: there was evidence for enhanced phase synchrony in right lateral frontal cortex after errors, and this measure predicted behavioral alteration in the upcoming trial differently for the two groups. The dissociations in brain-behavior relationships suggest that the GAD group exerted control differently, but not necessarily more or less efficiently, than the control group.

Theta Network Signals Boost Classification of GAD

A second stepwise regression was used to predict GAD, with independent variables from the previous stepwise regression (ERN and theta power) as well as indices of the theta band network features described in Figure 4 (theta ITPC, theta-RT correlation, theta ISPC, and ISPC-RT correlation). A three-factor solution accounted for 23% of the group variance (Supplemental Table S1). Adding onto the prior stepwise regression findings, the theta-RT correlation was the sole additional variable to account for significant discriminating variance.² Across the entire sample, greater anxious symptomatology as measured by the MASQ General Anxious Distress subscale significantly correlated with larger ERNs ($r_{78} = -.24$, $p = .035$) and the theta-RT relationship ($r_{78} = -.32$, $p = .005$), but not theta power ($r_{78} = .03$, $p = .80$).

Supplemental Figure S1 displays the accuracies of classification based on different algorithms, cross-validation measures, and feature inputs. In general, findings were robust to algorithms and cross-validation methods. While SVM classification based on power-RT correlations had the highest total accuracy (66.2%), this pattern was not robust when using LASSO (61.3%), and it had unimpressive sensitivity (53.6%). SVM classification based on all three measures (ERN, theta

power, and theta-RT β) provided the next highest total accuracy (65.2%), but ERN alone offered compelling stability across algorithmic approaches (SD was at most 50% the size of other feature variance). While these outcomes do not offer an objectively optimal discrimination, together they demonstrate the robustness of these measures.

DISCUSSION

In the current study, we demonstrated that both error-related and conflict-related ERPs (i.e., ERN and N2, respectively) differentiate subjects with GAD from control subjects; moreover, subjects with GAD were characterized by increased time-frequency representations of these effects (i.e., error-related and conflict-related theta, respectively). By leveraging multiple error-specific network activities, we accounted for 23% of the group variance and effectively classified patients with up to 66% accuracy. This more than doubles the amount of variance accounted for in previous work that used only ERN (9,10).

Midfrontal theta activities have been proposed to reflect a general mechanism for the realization and implementation of control (8). An enhanced theta response was common across psychological events requiring a need for control (i.e., errors and conflict) in subjects with GAD; yet, errors contained all the unique variance required to dissociate subjects with GAD from control subjects. While colinearity is an issue for multiple regressions, pattern classification of stimulus-locked activities was not as powerful as pattern classification of error-related activities.³ This error-specific dissociation suggests that the single psychological event of an error captures the common variance of anxiety-enhanced theta to varied signals of the need for control. Mechanistically, this offers an opportunity to probe the relationship between these error markers and the subsequent implementation of cognitive control.

At first glance, it may be surprising that ERN and theta power accounted for unique variance in subjects with GAD compared with control subjects. However, these are mathematically distinct manifestations that capture both common and unique neural activities. These ERP and time-frequency representations were not correlated with each other, and error-related ERPs and theta power accounted for significant independent variance in group differentiation. As an ERP component, the ERN captures temporally specific broad frequency enhancements, primarily theta and delta, that are phase locked across trials (19,24,25). As the modulus of the complex plane after wavelet convolution, theta power reflects total (phase-locked and non-phase-locked) amplitudes over a temporally smeared but more frequency-specific range. Thus, each method is uniquely effective at capturing aspects of a common underlying midfrontal theta dynamic that is altered in GAD.

Using a stepwise regression, we found that ERN alone provided the largest effect; however, error-related theta and theta-RT coupling provided additional and unique predictors of GAD status. Thus, multiple neural measures of error processing—derived from the same data—could be leveraged

²All analyses were rerun with a minimum of $n = 20$ errors to check if including participants with low trial count skewed the analyses (GAD group, $n = 26$, median errors = 34, interquartile range = 13; control group, $n = 35$, median errors = 43, interquartile range = 16). The statistical significance of group differences remains unchanged with a few exceptions. The Figure 1 error rate was diminished ($p = .01$) and post-error slowing was enhanced ($p = .01$) in the GAD group (but not post-error minus error RT, $p = .84$). The Figure 4 theta-RT relationship is similar but underpowered ($p = .20$), the Table 2 theta-RT relationship fails to add significant variance to the prior stepwise regression outputs. Classification accuracy remained at 62%–63% across the types of cross-validation methods used. These similarities suggest that these candidate biosignature findings are robust, even when behavioral differentiation is more volatile.

³All classification accuracies based on stimulus-locked activities were <61.8%.

to distinguish subjects with GAD from healthy control subjects. When ERN and error-related theta were combined with theta network activities involved in the implementation of control, classification was powerful (66% total accuracy), stable (high sensitivity and specificity), and robust (across cross-validation procedures, EEG feature selection, and number of errors). Diagnostically, this discriminant specificity of errors paves the way toward a plausible error-based biosignature for differentiating subjects with GAD from control subjects. Slight differences in algorithmic outputs are partially due to trial count: whereas the LASSO requires a second validation set (decreasing trials available for training), the SVM does not and thus benefits from more training data. These competing approaches are presented here to bolster future patient classification approaches: feature, algorithm, and cross-validation successes are likely to be dependent on each other, and it is beneficial to demonstrate the robustness of outcomes across a variety of approaches. A future endeavor may aim to leverage the strengths of varying algorithms to provide a single optimized approach.

Further evidence of specifically altered theta band activities in GAD was provided by the examination of the mediolateral frontal network involved in the implementation of cognitive control. The same network shown in Figure 4 has been advanced as a way to operationally define the mechanisms of cognitive control in this task (17). Mediolateral phase synchrony is a proposed mechanism for the communication of the need for control (8), and the enhancement of this feature in patients with GAD suggests an alteration in the implementation of cognitive control and not just a louder midfrontal “alarm bell” of ERN or theta power.

The degree of post-error adjustment was used as an objective indicator of cognitive control, and the GAD group indeed had altered brain-behavior dynamics compared with the control group. It is highly unlikely that the differential exertion of cognitive control described here could be identified using standard neuropsychological tasks of executive function. Indeed, even behavioral measures on this task could not differentiate the groups; only brain and brain-behavior relationships differentiated subjects with GAD from control subjects. Theta power predicted RT speeding versus slowing, whereas theta band phase synchrony predicted RT slowing versus speeding in subjects with GAD versus control subjects. It is hard to provide an a posteriori explanation for these dissociated outcomes, particularly as this type of trial-to-trial brain-behavior literature is quite sparse at the present time. Theta power has been shown to predict both post-error slowing (7) and post-error speeding (26) depending on task demands, demonstrating appropriate flexibility in the effective implementation of control. It is possible that this simple task had no overt optimal solution for control, so two systems responded differently to facilitate adjustment: with a reactive medial system and a proactive mediolateral system trading off in the adjustment of response readiness versus response caution. This is a testable hypothesis using the AX Continuous Performance Task (27–29) to assess reactive versus proactive control in anxiety.

In conclusion, this article aimed to advance beyond simple group differentiation, which is well represented in the biological psychiatric literature, toward a mechanistic and

diagnostic account of clinical cognitive neuroscience. The next challenge will be to test the ability of error-related EEG measures to sensitively and specifically dissociate GAD from other clinical groups and to account for demographically relevant moderators such as gender (30). We provide evidence that enhanced error signals in individuals with clinical anxiety are associated with an alteration in the implementation of cognitive control, and these combined features can discriminate patients from control subjects with impressive power, stability, and robustness. This approach to understanding cognitive control in anxiety is not only mechanistically revealing but also has compelling potential as a simple, fast, and inexpensive biosignature relevant to psychiatric practice.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the National Institute of General Medical Sciences Grant No. 1P20GM109089-01A1 (to JFC), National Institute of Mental Health Grant No. 1UH2MH109168-01 (to JFC), and National Institute on Alcohol Abuse and Alcoholism Grant No. R21AA0023947-01A1 (to JFC).

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychology (JFC), University of New Mexico, Albuquerque, New Mexico; Department of Psychology (AM), Florida State University, Tallahassee, Florida; and Department of Psychology (GH), Stony Brook University, Stony Brook, New York.

Address correspondence to James F. Cavanagh, Ph.D., Department of Psychology, University of New Mexico, Logan Hall, 1 University of New Mexico, MSC03 2220, Albuquerque, NM 87131; E-mail: jcavanagh@unm.edu.

Received Nov 30, 2016; revised Dec 27, 2016; accepted Jan 18, 2017.

Supplementary material cited in this article is available online at <http://dx.doi.org/10.1016/j.bpsc.2017.01.004>.

REFERENCES

- Moser JS, Moran TP, Schroder HS, Donnellan MB, Yeung N (2013): On the relationship between anxiety and error monitoring: A meta-analysis and conceptual framework. *Front Hum Neurosci* 7:466.
- Hajcak G (2012): What we've learned from mistakes: Insights from error-related brain activity. *Curr Dir Psychol Sci* 21:101–106.
- Gehring WJ, Goss B, Coles MGH, Meyer DE, Donchin E (1993): A neural system for error-detection and compensation. *Psychol Sci* 4: 385–390.
- Falkenstein M, Hohnsbein J, Hoormann J, Blanke L (1991): Effects of crossmodal divided attention on late ERP components. II. Error processing in choice reaction tasks. *Electroencephalogr Clin Neurophysiol* 78:447–455.
- Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S (2004): The role of the medial frontal cortex in cognitive control. *Science* 306: 443–447.
- Hajcak G, Foti D (2008): Errors are aversive: Defensive motivation and the error-related negativity. *Psychol Sci* 19:103–108.
- Cavanagh JF, Shackman AJ (2014): Frontal midline theta reflects anxiety and cognitive control: meta-analytic evidence. *J Physiol Paris* 109:3–15.
- Cavanagh JF, Frank MJ (2014): Frontal theta as a mechanism for cognitive control. *Trends Cogn Sci* 18:414–421.
- Weinberg A, Olvet DM, Hajcak G (2010): Increased error-related brain activity in generalized anxiety disorder. *Biol Psychol* 85:472–480.
- Weinberg A, Klein DN, Hajcak G (2012): Increased error-related brain activity distinguishes generalized anxiety disorder with and without comorbid major depressive disorder. *J Abnorm Psychol* 121:885–896.

11. First MB, Gibbon M, Spitzer RL, Williams JB, Benjamin LS (1996): Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV). Washington, DC: American Psychiatric Press, Inc.
12. Clark LA, Watson D (1991): Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *J Abnorm Psychol* 100:316–336.
13. Delorme A, Makeig S (2004): EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* 134:9–21.
14. Olvet DM, Hajcak G (2009): The stability of error-related brain activity with increasing trials. *Psychophysiology* 46:957–961.
15. Steele VR, Anderson NE, Claus ED, Bernat EM, Rao V, Assaf M, *et al.* (2016): Neuroimaging measures of error-processing: Extracting reliable signals from event-related potentials and functional magnetic resonance imaging. *Neuroimage* 132:247–260.
16. Pontifex MB, Scudder MR, Brown ML, O’Leary KC, Wu C-T, Themanson JR, Hillman CH (2010): On the number of trials necessary for stabilization of error-related brain activity across the life span. *Psychophysiology* 47:767–773.
17. Cavanagh JF, Cohen MX, Allen JJB (2009): Prelude to and resolution of an error: EEG phase synchrony reveals cognitive control dynamics during action monitoring. *J Neurosci* 29:98–105.
18. Cohen MX, Cavanagh JF (2011): Single-trial regression elucidates the role of prefrontal theta oscillations in response conflict. *Front Psychol* 2:30.
19. Cavanagh JF, Zambrano-Vazquez L, Allen JJB (2012): Theta lingua franca: A common mid-frontal substrate for action monitoring processes. *Psychophysiology* 49:220–238.
20. Cohen MX (2014): *Analyzing Neural Time Series Data: Theory and Practice*. Cambridge, MA: MIT Press.
21. Dutilh G, Vandekerckhove J, Forstmann BU, Keuleers E, Brysbaert M, Wagenmakers E-J (2012): Testing theories of post-error slowing. *Atten Percept Psychophys* 74:454–465.
22. Tibshirani R (1994): Regression selection and shrinkage via the lasso. *J R Statist Soc B* 73:273–282.
23. Cavanagh JF, Castellanos J (2016): Identification of canonical neural events during continuous gameplay of an 8-bit style video game. *Neuroimage* 133:1–13.
24. Cohen MX, Donner TH (2013): Midfrontal conflict-related theta-band power reflects neural oscillations that predict behavior. *J Neurophysiol* 110:2752–2763.
25. Yordanova J, Falkenstein M, Hohnsbein J, Kolev V (2004): Parallel systems of error processing in the brain. *Neuroimage* 22:590–602.
26. Narayanan NS, Cavanagh JF, Frank MJ, Laubach M (2013): Common medial frontal mechanisms of adaptive control in humans and rodents. *Nat Neurosci* 16:1888–1895.
27. Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998): Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280:747–749.
28. Cohen JD, Barch DM, Carter C, Servan-Schreiber D (1999): Context-processing deficits in schizophrenia: Converging evidence from three theoretically motivated cognitive tasks. *J Abnorm Psychol* 108:120–133.
29. Cohen JD, Perstein WM, Braver TS, Nystrom LE, Noll DC, Jonides J, Smith EE (1997): Temporal dynamics of brain activation during a working memory task. *Nature* 386:604–608.
30. Moser JS, Moran TP, Kneip C, Schroder HS, Larson MJ (2016): Sex moderates the association between symptoms of anxiety, but not obsessive compulsive disorder, and error-monitoring brain activity: A meta-analytic review. *Psychophysiology* 53:21–29.