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Considering ERP difference scores as individual difference measures: Issues with subtraction and alternative approaches

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Abstract

There is growing interest in psychophysiological and neural correlates of psychopathology, personality, and other individual differences. Many studies correlate a criterion individual difference variable (e.g., anxiety) with a psychophysiological measurement derived by subtracting scores taken from two within-subject conditions. These subtraction-based difference scores are intended to increase specificity by isolating variability of interest. Using data on the error-related negativity (ERN) and correct response negativity (CRN) in relation to generalized anxiety disorder (GAD), we highlight several conceptual and practical issues with subtraction-based difference scores and propose alternative approaches based on regression. We show that ERN and CRN are highly correlated, and that the ΔERN (i.e., ERN − CRN) is correlated in opposite directions both with ERN and CRN. Bivariate analyses indicate that GAD is related to ΔERN and ERN, but not CRN. We first show that, by using residualized scores, GAD relates both to a larger ERN and smaller CRN. Moreover, by probing the interaction of ERN and CRN, we show that the relationship between GAD and ERN varies by CRN. These latter findings are not evident when using traditional subtraction-based difference scores. We then completed follow-up analyses that suggested that an increased P300 in anxious individuals gave rise to the apparent anxiety/CRN relationship observed. These findings have important conceptual implications for facilitating the interpretability of results from individual difference studies of psychophysiology.

Descriptors: Cognition, Sensation/perception, EEG, Young adults, Psychophysics, Visual processes

The scientific study of neural function, and psychophysiology more broadly, involves comparing two or more experimental conditions—a foundation based on within-subject differences. In the simplest case, a dependent measure is contrasted between two conditions—and the resulting difference is interpreted as reflecting some specific cognitive or affective process or function. As an example, the response-locked ERP differs following error compared to correct responses to task stimuli; the increased negativity after errors (i.e., the error-related negativity or ERN) relative to a much smaller correct response negativity (CRN) is thought to reflect the processing of errors (see Figure 1; Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993).

Indeed, within-subject manipulations that render errors more important will increase the ERN: providing subjects with instructions that emphasize accuracy over speed (Gehring et al., 1993), making errors more valuable (Hajcak, Moser, Yeung, & Simons, 2005), and punishing errors (Riesel, Weinberg, Endrass, Kathmann, & Hajcak, 2012) all potentiate the ERN. Again, these studies involve a within-subject comparison: contrasting the ERN obtained in one condition with another. Based in part on these within-subject data, we have argued that variation in the ERN reflects the relative importance of errors (Hajcak, 2012; Proudfit, Inzlicht, & Mennin, 2013).

Variation in the ERN has also been examined in terms of between-subjects differences (Weinberg, Riesel, & Hajcak, 2012). One robust finding is that the ERN is larger among individuals who are more anxious. Indeed, a recent meta-analysis suggests that anxiety is related to a larger ERN but not CRN (Moser, Moran, Schroder, Donnellan, & Yeung, 2013). The meta-analysis also found that anxiety was related to a larger difference between the ERN and CRN (i.e., ΔERN)—further suggesting that anxiety relates specifically to error-related brain activity.

The logic of examining a difference-based measure such as the ΔERN is intuitive: we may be drawn to focus on difference scores precisely because it is a difference between conditions that isolated a process of interest in the first place. We may want to "control for" between-subjects variability that is unrelated to a specific process. Practically, we know that ERP measures often reflect

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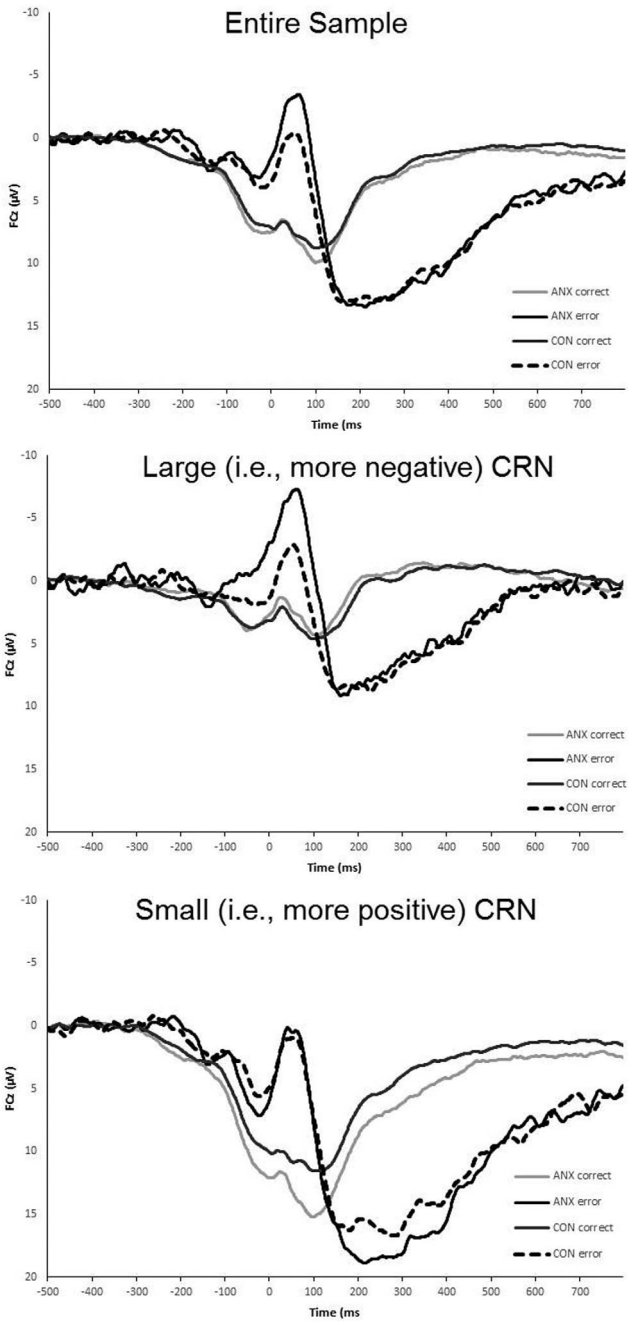

Figure 1. Response-locked ERP waveforms for correct and error trials. On the top, waveforms are depicted for the whole sample. For representation purposes, a mean-split was performed on CRN magnitude—wherein participants with a larger (i.e., more negative) CRN are depicted in the middle and participants with a smaller (i.e., less negative) CRN are depicted on the bottom.

overlapping processes, and thus the difference measure method should presumably isolate neural activity related to a specific process (Kappenman & Luck, 2011). Indeed, several ERPs are defined as the difference between two within-subject conditions (e.g., the N2pc, which is quantified as the difference between contralateral and ipsilateral activity; the lateralized readiness potential, which is quantified by subtracting ipsilateral from contralateral voltage, relative to the response hand; Luck, 2005).

In terms of the ΔERN, subtracting the CRN from the ERN is done to isolate neural activity specific to error processing (i.e., eliminate activity common to both error and correct trials). In regard to Figure 1, the ERN is a relative negativity following error trials—though there is a similar but smaller negativity on correct trials. It is possible that all responses elicit a CRN and that the ERN reflects an additional process specific to errors (Vidal, Hasbroucq, Grapperon, & Bonnet, 2000). In this way, the CRN can be thought of as a type of baseline on which the ERN sits. In this case, the additional increase of error compared to correct trials is reflected in the ΔERN. That is, if the CRN were relatively small or large, a similar-sized ERN would be associated with a larger or smaller ΔERN, respectively. The difference score, therefore, is intended to account for the way in which the magnitude of the CRN would impact the interpretation of the ERN. In regard to individual differences studies, the ERN, the CRN, and the ΔERN are then examined in relation to other measures of individual differences (e.g., self-report, age). This amounts to moving from within-subject change (i.e., a more negative ERN than CRN) to between-subjects comparisons (i.e., a more negative ERN and ΔERN have been related to increased anxiety; Moser et al., 2013).

The current paper explores subtraction-based difference scores in ERP research that focuses on individual differences—and to do so, we continue to focus on the ERN, CRN, and ΔERN in relation to clinically diagnosed generalized anxiety disorder (GAD). We emphasize, however, that the conceptual issues apply to all psychophysiological studies that correlate individual difference measures with subtraction-based difference scores—a practice that is actually quite common. For instance, recent studies in emotion often subtract neutral from emotional condition averages to quantify individual differences in emotional reactivity (Angus, Kemkes, Schutter, & Harmon-Jones, 2015; Bress, Meyer, & Hajcak, 2015; Burkhouse, Siegle, Woody, Kudinova, & Gibb, 2015; Hoenen, Lübke, & Pause, 2015; Kornilov, Magnuson, Rakhlin, Landi, & Grigorenko, 2015; McTeague, Lang, Laplante, & Bradley, 2011; Meyer, Hajcak, Torpey-Newman, Kujawa, & Klein, 2015; Sylvester, Hudziak, Gaffrey, Barch, & Luby, 2015). Indeed, current recommendations from experts in the field involve "isolating components of interest by creating [subtraction-based] difference waves" (Luck, 2014). Thus, the aim here is to elucidate common, domain-general statistical properties of difference score calculation that may affect their interpretation by illustrating these properties via data on the ERN in relation to GAD.

One issue with most psychophysiological measures is that, even though two condition-related averages may differ from one another (i.e., the ERN is more negative than the CRN), they tend to be highly correlated across individuals (e.g., subjects with a more negative ERN will tend to have a more negative CRN). This is not specific to the ERN. For instance, the difference between the ERP response to monetary gains and losses has been described as reflecting a feedback negativity (FN) or reward positivity; however, the ERP responses to monetary gains and losses are highly correlated (e.g., .74) across subjects (Bress, Smith, Foti, Klein, & Hajcak, 2012). Thus, difference scores are often based on subtracting highly correlated variables.

As described above, the CRN (i.e., the subtrahend) is subtracted from the ERN (i.e., the minuend) to yield the ΔERN (i.e., the difference). The goal is to control for neural activity common to both error and correct trials and to isolate error-specific neural activity. However, the result of a subtraction (the difference) is not independent from the subtrahend and minuend: the ΔERN will be correlated both with the CRN and ERN, but in opposite directions.

Thus, subtraction-based difference measures are correlated with both constituent measures. The ΔERN is not, therefore, a measure of error processing that is independent of the CRN. In other words, based purely on the mathematical features of the ΔERN, one cannot straightforwardly interpret effects associated with it in the fashion that seems most intuitive: the effect is not purely associated with the magnitude of the difference between ERN and CRN.

In fact, the only way that subtraction-based difference measures (e.g., the ΔERN) can correlate more strongly with a criterion measure (e.g., anxiety) than the CRN or ERN alone is if the constituent scores (e.g., ERN and CRN) correlate in opposite directions with the criterion measure (Edwards, 1994; Laird & De Los Reyes, 2013; Laird & LaFleur, 2014; Laird & Weems, 2011). Consider the case in which CRN is perfectly uncorrelated with anxiety: the ΔERN and ERN correlations with anxiety will then be identical; the only way for the criterion/ΔERN correlation to exceed the correlation with ERN is if the criterion and CRN are correlated in the opposite direction. If this is the case, then the subtraction-based correlation is conflating two effects (i.e., a correlation between anxiety and ΔERN could reflect a correlation between anxiety and ERN in one direction and the correlation between CRN and anxiety in the opposite direction). Finally, the subtraction-based difference approach ignores potential suppressor effects. That is, if CRN and ERN are correlated with one another but related to the criterion in opposite directions, then the unique potential relationships between these variables can only be suppressed in bivariate correlations.

Our goal with the current paper is to illustrate these issues and offer well-known regression-based statistical tools (residual difference scores and interaction terms) as an alternative to traditional subtraction-based difference score measures. In particular, we begin by considering difference scores based on measuring the variance leftover in a regression equation in which one models one score (e.g., CRN) as a predictor of another score (e.g., ERN; i.e., regression residuals or residualized scores). Using data from published studies on the ERN and using GAD as a criterion variable, we demonstrate how residualized scores produce a difference measure that is uncorrelated with CRN (i.e., a unique measure of error processing). Further, we illustrate how residualized scores reveal a relationship between CRN and GAD not apparent in bivariate correlations. Finally, we illustrate a regression-based approach that includes an interaction term (i.e., CRN × ERN) as a means of testing the "intuitive" interpretation mentioned above: whether the relationship between ERN and GAD depends on level of CRN. This regression-based approach simultaneously captures residualized difference-score measurement, and tests whether associations are conditional (i.e., whether the link between ERN and GAD varies across CRN levels). These three illustrations are used to demonstrate the limits of interpretation, and situation-specific utility, of each of these methods.

Method

Participants

The current study combined participants from two separate previously published studies that examined ERN in relation to GAD (Weinberg, Klein, & Hajcak, 2012; Weinberg, Olvet, & Hajcak, 2010). The current study focuses on 41 participants with a diagnosis of GAD (but not comorbid depression) and 53 individuals with no current DSM diagnosis (i.e., healthy controls, HC). All diagnoses were made using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM) 4th edition (SCID; Spitzer, Williams, Gibbon, & First, 1992). For additional information on recruiting and patient information, see Weinberg et al. (2010).

Task and Materials

An arrow version of the flanker task (Eriksen & Eriksen, 1974) was administered on a Pentium D class computer, using Presentation software (Neurobehavioral Systems, Inc., Albany, CA) to control the presentation and timing of all stimuli. Each stimulus was displayed on a 19" (48.3-cm) monitor. On each trial, five horizontally aligned arrowheads were presented. Half of all trials were compatible (< < < < < or > > > > >) and half were incompatible (< < > < < or > > < > >). The order of compatible and incompatible trials was random. Each set of arrowheads occupied approximately 1.3° of visual angle vertically and 9.2° horizontally. All stimuli were presented for 200 ms followed by an intertrial interval that varied randomly from 2,300 to 2,800 ms.

Procedure

Following informed consent and a brief description of the experiment, EEG electrodes were attached, and the subject was given detailed task instructions. All participants performed multiple tasks during the experiment. The order of the tasks was counterbalanced across participants, and the results of other tasks will be reported elsewhere. Participants were seated at a viewing distance of approximately 24″ (61 cm) and were instructed to press the right mouse button if the center arrow was facing to the right and to press the left mouse button if the center arrow was facing to the left. Information about each response (e.g., reaction time, accuracy) was recorded. Participants performed a practice block containing 30 trials during which they were instructed to be both as accurate and fast as possible. The actual task consisted of 11 blocks of 30 trials (330 trials total) with each block initiated by the participant. Participants received feedback based on their performance at the end of each block. If performance was 75% correct or lower, the message "Please try to be more accurate" was displayed. Performance above 90% correct was followed by "Please try to respond faster." If performance was between 75 and 90% correct, the message "You're doing a great job" was displayed.

Psychophysiological Recording, Data Reduction, and Analysis

Continuous EEG recordings were collected using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). Thirty-four electrode sites were used, based on the 10/20 system, as well as two electrodes on the right and left mastoids. The electrooculogram (EOG) generated from eye movements and eyeblinks was recorded using four facial electrodes: horizontal eye movements (HEM) were measured via two electrodes located approximately 1 cm outside the outer edge of the right and left eyes, vertical eye movements (VEM) and blinks were measured via two electrodes placed approximately 1 cm above and below the right eye. The EEG signal was preamplified at the electrode to improve the signal-to-noise ratio by a BioSemi ActiveTwo system. The data were digitized at 24-bit resolution with a least significant bit (LSB) value of 31.25 nV and a sampling rate of 1024 Hz, using a low-pass fifth-order sinc filter with -3 dB cutoff point at 208 Hz. Each active electrode was measured online with respect to a common mode sense (CMS) active electrode, located between PO3

and POz, producing a monopolar (nondifferential) channel. CMS forms a feedback loop with a paired driven right leg (DRL) electrode. Offline, all data were referenced to the average of the left and right mastoids, and band-pass filtered with low and high cutoffs of 0.1 and 30 Hz, respectively. Eyeblink and ocular corrections were conducted using both VEM and HEM channels per a modification of the original algorithm published in Gratton, Coles, and Donchin (1983).

A semiautomatic procedure was employed to detect and reject artifacts. Data from individual channels were rejected if a voltage step of more than 50.0 μV between sample points or a voltage difference of 300.0 μV within a trial existed. In addition, data were identified as artifacts if a voltage difference of less than .50 μV within 100-ms intervals was present. Visual inspection of the data was then conducted to detect and reject any remaining artifacts.

The EEG was segmented for each trial beginning 500 ms before response onset and continuing for 1,500 ms (i.e., 1,000 ms following the response); a 200-ms window from −500 to −300 ms before the response onset served as the baseline. Correct and error trials were averaged separately. The ERN and CRN were scored as the average activity from 0 to 100 ms at FCz, following error and correct responses, respectively.

As part of follow-up analyses (explained in more detail below), we also measured the stimulus-locked P300. The EEG was segmented for each trial beginning 200 ms before stimulus onset and continuing for 1,200 ms (i.e., 1,000 ms following the stimulus); a 200-ms window from −200 to 0 ms before the stimulus onset served as the baseline. The P300 was scored as the average activity from 300–600 ms at FCz on compatible correct trials.

Additionally, as part of follow-up analyses, we analyzed these data in the time-frequency domain. To compute the power of oscillatory activity, a current source density transform was applied to the data. The time-frequency analysis was conducted by applying a continuous wavelet transform using complex Morlet wavelets (Lachaux, Rodriguez, Martinerie, & Varela, 1999; Samar, Bopardikar, Rao, & Swartz, 1999). The complex Morlet wavelet is defined by the following formula:

$$\Psi(t,f) = Ae^{-t^2/2\sigma_t^2} e^{i2\pi ct}$$

In the formula, t is time, e is the base of the natural logarithm, and f is the frequency, which increased from 1 to 30 Hz in 20 logarithmic steps. Factor A is the normalization parameter. Parameter c determines the number of oscillations of the wavelet. The complex Morlet transform was applied with $c = 4$ to provide an adequate tradeoff between temporal and frequency resolution. A 300-ms time window preceding the flanker stimuli was used for normalization (i.e., Gabor normalization). Theta activity was scored by extracting the wavelet power between 4 and 8 Hz from the averages for correct and erroneous responses from 0–100 ms after the response at FCz.

Data Analytic Plan

In the current study, we sought to compare a traditional subtraction-based difference score approach to an alternative approach utilizing regression-based difference scores. To do so, we first completed a mixed model analysis of variance (ANOVA) wherein response was entered as a within-subject variable (ERN, CRN) and clinical group was entered as a between-subjects variable (GAD, HC). We then completed post hoc t tests to examine whether the ERN, CRN, or ΔERN (i.e., the ERN minus the CRN, the traditional subtraction-based difference score) differed between the groups. Next, we completed correlations between the ERN, CRN, ΔERN, and clinical group. We utilized Pearson correlations: those between continuous variables are product-moment correlations, whereas the correlations with the categorical GAD variable are point-biserial correlations.

Table 1. *Means (Standard Deviations) for the Healthy Control and Anxious Groups*

	ERN	CRN	ΔERN
HC ($N = 53$)	1.56[a] (5.28)	7.17 (4.39)	−5.61[b] (5.17)
GAD ($N = 41$)	−.63[a] (6.25)	8.29 (6.99)	−8.92[b] (4.49)

Note. HC = healthy control; GAD = generalized anxiety disorder; ERN = error-related negativity; CRN = correct response negativity; ΔERN = subtraction-based differences score (error minus correct).
[a]$p < .10$. [b]$p < .01$.

As an alternative to the subtraction-based difference score, we created the ERN_{resid} by saving the variance leftover in a regression equation wherein the CRN was entered predicting the ERN. Likewise, we created the CRN_{resid} by saving the variance leftover in a regression equation wherein the ERN was entered predicting the CRN. We then completed correlations to examine the associations between the residualized scores and the ERN, CRN, and clinical group. To examine whether the relationship between the ERN and anxiety was conditional upon the level of the CRN, we completed a logistic regression wherein the mean-centered ERN and CRN, as well as their interaction (ERN × CRN), were all entered predicting clinical group (GAD, HC).

Results

The means and standard deviations for ERN, CRN, and ΔERN for GAD and HC participants are presented in Table 1. Response-locked ERP waveforms for correct and error trials for the GAD and HC groups are depicted at the top of Figure 1. A 2 (Group: GAD, HC) × 2 (Response: error, correct) mixed model ANOVA confirmed that the ERN was more negative than the CRN, $F(1,92) = 204.53$, $p < .001$; although GAD and HC did not differ overall, $F(1,92) < 1$, there was a significant interaction between response and group, $F(1,92) = 10.59$, $p < .01$. Post hoc independent samples t tests suggest that the GAD group was characterized by a more negative ERN at a trend level, $t(92) = 1.84$, $p < .10$; the GAD group had a nonsignificantly more positive CRN, $t(92) < 1$; and the ΔERN was more negative for the GAD group than the HC group, $t(92) = 3.25$, $p < .01$.

Table 2 presents correlations between GAD/HC status, ERN, CRN, and ΔERN. CRN and ERN were moderately correlated, $r(92) = .60$, $p < .05$, and ΔERN was correlated both with ERN, $r(92) = .47$, $p < .05$, and CRN, $r(92) = -.43$, $p < .05$. GAD status was related to a larger (i.e., more negative) ERN at a trend level, and a smaller (i.e., more positive) CRN—though this latter relationship did not reach significance. However, GAD status significantly related to ΔERN. Thus, ΔERN was not independent of ERN or CRN—and GAD predicted a more negative ΔERN because GAD was associated with a more negative ERN and a more positive CRN. The GAD/ΔERN relationship was evinced because it capitalized on the opposite relationship between GAD and ERN/CRN.

Next, we created residualized CRN and ERN scores. To create ERN_{resid}, unstandardized residuals were saved predicting ERN from CRN using a linear regression. Along the same lines, CRN_{resid} was created by predicting CRN from the ERN, and saving the unstandardized residuals. Table 2 presents correlations between

Table 2. *Correlations Between GAD Status, ERN, CRN, and ΔERN*

	GAD	ERN	CRN	ΔERN	ERN_{resid}
GAD	–	–	–	–	–
ERN	.19^{+}	–	–	–	–
CRN	−.10	.60**	–	–	–
ΔERN	.32**	.47**	−.43**	–	–
ERN_{resid}	.31**	.80**	0	.91**	–
CRN_{resid}	−.26**	0	.80**	−.88**	−.60**

Note. All values are two-tailed. Pearson correlations—those between continuous variables are product-moment correlations, while the correlations with the categorical GAD variable is a point-biserial correlation. GAD = generalized anxiety disorder (the clinical group); ERN = error-related negativity; CRN = correct response negativity; ΔERN = subtraction-based differences score (error minus correct); ERN_{resid} and CRN_{resid} = residualized scores.
$+p < .10$. $**p < .01$.

CRN_{resid}, ERN_{resid}, and other measures. ERN_{resid} is positively correlated with ERN, but uncorrelated with CRN; CRN_{resid} is positively correlated with CRN but uncorrelated with ERN. Both ERN_{resid} and CRN_{resid} are highly correlated with ΔERN, in opposite directions. Upon controlling for CRN, GAD is significantly related to a larger ERN_{resid}; similarly, after controlling for the ERN, GAD is related to a smaller CRN_{resid}. In this way, residualized scores suggest a significant relationship between GAD and both ERN and CRN—and a suppressor effect whereby these associations are not evident in bivariate correlations.

Finally, we used logistic regression to predict GAD status based on the mean-centered ERN, the mean-centered CRN, and their interaction (Table 3). Both ERN and CRN exhibit main effects in this model, such that both more positive (i.e., smaller) CRN and more negative (i.e., bigger) ERN are both independently related to a greater likelihood of GAD, $OR = 1.13$ and .87, respectively. This is identical to the residual effect described above. However, the significant interaction term indicates that there is also a contingent relationship in addition to these main effects. Specifically, considering CRN as the moderator, a more negative (larger) ERN predicts a greater likelihood of GAD at the mean of CRN (main effect of ERN in Table 3) and 1 *SD* below the mean (i.e., a larger CRN; $B = -.23$, $OR = .79$, $p < .001$), but not at 1 *SD* above the mean (i.e., a smaller CRN; $B = -.04$, $OR = .96$, $p = .55$).

As demonstrated in Figure 2, this means that the likelihood of receiving a GAD diagnosis does not vary as a function of ERN when CRN is more positive (likelihoods of .58 and .46 for large and small ERN, respectively); however, when CRN is large (more negative), there is a relative reduction in likelihood under conditions of small ERN (likelihoods of .52 and .07 for large and small ERN, respectively). In other words, in the condition in which the difference between ERN and CRN is smallest, one is significantly less likely to receive a GAD diagnosis. This same pattern can also been seen in the ERP waveforms in the middle and bottom of Figure 1—wherein the sample was mean-split based on CRN magnitude. As can be seen in the figure, among individuals with a large (more negative) CRN, a larger ERN is associated with a GAD diagnosis. However, among individuals with a small (less negative) CRN, the ERN does not relate to diagnostic status.

Follow-Up Analyses

The interaction can also be stated another way: among individuals with a small (more positive) ERN, a small (more positive) CRN is associated with GAD diagnostic status. This finding, along with the finding that GAD is associated with a smaller CRN_{resid} across the sample, was unexpected given that a recent meta-analysis suggests that the CRN magnitude is not associated with anxiety (Moser et al., 2013). Furthermore, in studies that have found anxiety/CRN relationships, they have predominately found an increased CRN among anxious individuals (Riesel, Endrass, Kaufmann, & Kathmann, 2011; Xiao et al., 2011).

Table 3. *Logistic Regression Predicting Likelihood of a Generalized Anxiety Disorder Diagnosis from ERN, CRN, and their Interaction*

Variable	*B* (*SE*)
Constant	−.59* (.26)
ERN	−.14* (.06)
CRN	.12* (.06)
ERN × CRN	.02* (.01)
Cox and Snell R^2	.16
Nagelkerke R^2	.21

Note. ERN = error-related negativity; CRN = correct response negativity; OR = odds ratio.
$*p < .05$.

Visual inspection of the ERP waveforms in Figure 1 (bottom) suggest that, while the GAD group was characterized by a more positive (smaller) CRN, they also appeared to be characterized by equally more positive neural activity in the time window after the CRN. Indeed, an independent samples *t* test suggested that, among individuals with a "small/more positive ERN" (based on a mean-split), those with GAD were characterized by a more positive CRN, $t(48) = 3.6$, $p < .01$, and more positive neural activity during a later time window (i.e., 200–400 ms), $t(48) = 1.87$, $p = .06$—during both error, $t(48) = 1.60$, $p = .10$, and correct trials, $t(48) = 1.71$, $p = .09$, at a trend level. Given that the ERN sits on top of a larger stimulus-locked positivity (i.e., P300; Hajcak, Vidal, & Simons, 2004), we hypothesized that it was variation in this broad positivity that may underlie findings from the ERN × CRN interaction.

Indeed, when we examined the stimulus-locked P300, results suggested that, among individuals with a small ERN, those with GAD were characterized by an increased (i.e., more positive)

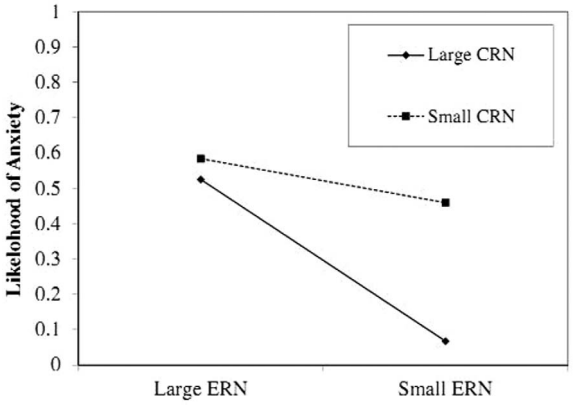

Figure 2. Illustration of the CRN-contingent effect of ERN on likelihood of receiving a GAD diagnosis, as demonstrated in the moderation model. Large and small values are ± 1 *SD* from the mean of each. ERN = error-related negativity; CRN = correct response negativity.

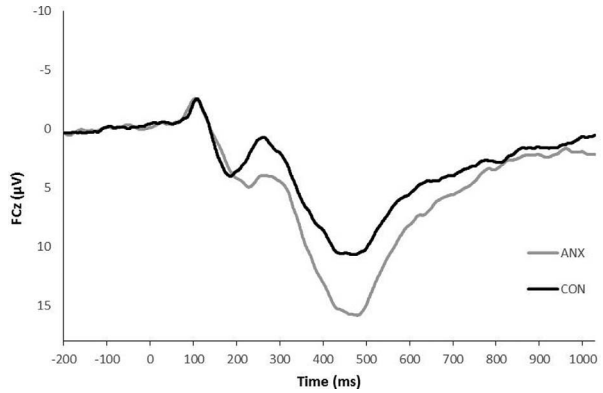

Figure 3. Stimulus-locked waveforms for congruent trials. For representation purposes, a mean-split was performed on ERN magnitude—wherein participants with a smaller (i.e., more positive ERN) are depicted in this figure.

P300, $t(48) = 2.69$, $p < .01$, GAD group: $M = 21.29$, $SD = 7.62$, HC group: $M = 15.77$, $SD = 6.47$ (see Figure 3).

To explore this possibility in the full sample, we completed a logistic regression wherein the ERN, CRN, and P300, as well as their two-way and three-way interactions, were entered predicting diagnostic status. In this model, only the interaction between the ERN and P300 was significant, at a trend level, $OR = 1.03$, $p = .07$, such that the ERN related to diagnostic status when the P300 was at mean level or one *SD* below the mean (i.e., less positive), $ps < .01$. However, when the P300 was large (i.e., more positive), the ERN no longer related to GAD status, $p = .29$. The interaction can also be stated in the following way: GAD status was related to an increased P300, but only when the ERN was relatively small (i.e., less negative), $p < .05$. In this model, none of the other main effects or interactions were significant, all $ps > .20$.

To further explore this possibility, we analyzed these data in the time-frequency domain. Previous work suggests that, whereas the P300 emerges from increases in theta, delta, and alpha oscillatory activity (Kolev, Demiralp, Yordanova, Ademoglu, & Isoglu-Alkaç, 1997; Yordanova, Devrim, Kolev, Ademoglu, & Demiralp, 2000), the ERN appears to be more specifically linked to midline activity in the theta range (Cavanagh & Shackman, 2014; Cavanagh, Zambrano-Vazquez, & Allen, 2012; Munneke, Nap, Schippers, & Cohen, 2015). Theta activity was scored by extracting the power between 4 and 7 Hz from the averages for correct and erroneous responses. After doing so, we used the correct-related theta activity and error-related theta activity, and their interaction to predict diagnostic status. In this model, increased error-related theta activity was associated with GAD status, $OR = 1.50$, $p < .05$. However, neither correct-related theta nor the interaction significantly predicated diagnostic status, both $ps > .8$.

Discussion

The current investigation sought to explore an alternative to traditional subtraction-based difference scores by utilizing residual difference scores and interaction terms. We demonstrated that, while the ERN and CRN are correlated, we can use a residual score to produce a difference measure that is uncorrelated with the CRN—and is therefore a unique measure of error processing. Additionally, by using a residualized score, we were able to observe a relationship between the CRN and anxiety that was not apparent in bivariate correlations. Furthermore, by including an interaction term (i.e., ERN × CRN), we found that the relationship between the ERN and anxiety depends on the magnitude of the CRN. Using this method, we observed a contingent association between the CRN and anxiety that was unexpected: among individuals with a small ERN, anxiety was associated with a smaller (more positive) CRN. To better understand this effect, we completed follow-up analyses that suggested that an increased P300 in anxious individuals gave rise to the apparent anxiety/CRN relationship observed. Hence, using a residualized approach, we were able to uncover novel findings regarding the relationship between anxiety and neural processes that were imperceptible using the traditional difference score approach.

Using the traditional subtraction-based difference score approach to these data suggested that individuals with GAD were characterized by a larger ΔERN (error minus correct activity). However, because the ΔERN is correlated with both the ERN and CRN in opposite directions, it is not a specific measure of error processing, and thus interpretation of this finding is unclear. Using a residual-based approach, we were able to obtain measures that specifically indexed error- and correct-related neural activity; the ERN_{resid} was correlated to the ERN, but not CRN, whereas the CRN_{resid} was correlated to the CRN, but not the ERN. In doing so, we created a more readily interpretable measure, and found that the ERN_{resid} and CRN_{resid} related to GAD status in the opposite direction—a pattern that was not evident in the bivariate associations using the ERN, CRN, or the subtraction-based ΔERN.

We then used a regression-based approach that included an interaction term (ERN × CRN) to isolate the unique relationship between ERN and GAD diagnosis as a function of CRN (i.e. the "intuitive" interpretation of a difference score). We found that, among individuals with a large (more negative) CRN, a larger ERN was associated with a GAD diagnosis. However, among individuals with a small (less negative) CRN, the ERN did not relate to diagnostic status. In other words, the relationship between the ERN and anxiety was only evident when the level of the CRN was in a specific range (i.e., average to large). Using the regression-based approach, we were able to go beyond what the subtraction-based difference score provided by illustrating the way in which observed associations were conditional, and much more circumscribed (i.e., did not apply to the full range of ERP responses to trials) than was evident via examination of subtraction-based difference scores alone. While the finding that the ERN is increased in anxious individuals is consistent with previous literature (Moser et al., 2013), the notion that this relationship may be contingent upon the level of the CRN is a novel finding.

Previous work suggests that the CRN magnitude is not associated with anxiety (Moser et al., 2013), and when studies have found a relationship, they have typically found an increased CRN among anxious individuals (Riesel et al., 2011; Xiao et al., 2011). In this context, our finding that anxiety was associated with a smaller (more positive) CRN_{resid} across the sample, as well as the significant interaction between CRN and ERN in predicting GAD status (i.e., among individuals with a small ERN, a small CRN was associated with GAD status) were surprising. However, none of the previous studies have utilized a residualized approach or examined the interaction between the ERN and CRN; given that the CRN and ERN are highly correlated, it is possible that these effects were evident in these previous datasets, but were not available via traditional difference score techniques.

In the current study, visual inspection of the ERP waveforms suggested that the GAD group was characterized by a more positive CRN, and equally more positive neural activity in the time window after the CRN. We hypothesized that an increased

stimulus-locked P300 among anxious individuals may underlie what appeared to be a more positive CRN. Indeed, in a model including the CRN, ERN, and P300, only the interaction between the P300 and ERN approached significance—suggesting that an increased ERN related to diagnostic status when the P300 was relatively small. And, an increased P300 was related to diagnostic status when the ERN was relatively small. In other words, the association between the ERN and anxiety might really be contingent upon the P300. Because these effects are in opposite directions, they suppress each other. For example, in the group of individuals with more positive (smaller) CRN (see bottom of Figure 1), neural activity on both error and correct trials appears to be more positive in the GAD group. This enhanced positivity is likely due to an increased stimulus-locked P300 rather than response-locked differences. If the impact of the P300 were removed, both the error and correct waveforms in the GAD group would presumably be shifted in the negative direction; in this case, an increased ERN in the GAD group would be evident, similar to what is found in individuals with a larger (more negative) CRN (Figure 1, middle). In other words, an increased P300 in anxious individuals can mask increased error-related neural activity. Further consistent with this possibility, when theta activity (which is more independent of the P300) was extracted from the averages for correct and error responses, only error-related theta activity related to GAD status.

To our knowledge, no previous study has examined the interaction between error processing and the P300 in relation to individual differences in anxiety. Some previous work has found an increased P300 in anxious individuals (Ischebeck, Endrass, Simon, & Kathmann, 2011; Miltner et al., 2005; Simons, 2010; Wang et al., 2013), while other work has not (Howe, Pinto, & De Luca, 2014; Kıvırcık, Yener, Alptekin, & Aydın, 2003; Sachs et al., 2004). To our knowledge, no previous study has examined the relationship between the P300 elicited by flanker stimuli and anxiety; most studies have focused on the P300 in response to emotional stimuli (e.g., images of spiders in spider phobics). The P300 waveform is thought to reflect information processing and attentional resource allocation (Donchin, 1987; Picton, Hillyard, Krausz, & Galambos, 1974) and perhaps a neural mechanism to inhibit extraneous brain activation (Polich, 2007). Some have posited that anxiety is related to decreased goal-driven attentional control and increased stimulus-driven attentional capture (Eysenck, Derakshan, Santos, & Calvo, 2007)—which may be reflected, in part, by the increased P300 to flanker stimuli observed among anxious individuals in the current study. Future work should investigate this possibility—especially in light of the fact that stimulus-related neural activity that overlaps with response-related activity may relate to anxiety in the opposite direction and thereby suppress our ability to detect these relationships.

The current findings also have broader implications for individual difference work that utilizes psychophysiological measures within stimulus/response paradigms. In the current study, response-related neural activity overlapped with neural activity elicited by the imperative stimulus. Individual differences may relate to response and stimulus processing differentially and in complex ways. Indeed, one recent study found that a mindset manipulation impacted error and stimulus processing of flanker stimuli in unexpected and opposing ways (Schroder, Moran, Donnellan, & Moser, 2014). Other psychophysiological work that includes overlapping or sequential events (e.g., startle probes presented following affective picture presentations) might also consider whether individual differences in one measure are accounted for by another.

Techniques from clinical neuroscience are increasingly being used to study dysfunction underlying psychopathology; indeed, the National Institute of Mental Health's Research Domain Criteria (RDoC) initiative is an effort to develop and utilize reliable measures of well-validated process constructs (i.e., domains) as a foundation for clinical research (Cuthbert, 2014). The ERN currently appears as a unit of measurement in multiple RDoC domains and has been associated with variability in anxious and depressive symptoms (Weinberg et al., 2016). In the current study, we utilized the ERN to illustrate measurement issues that would apply to any unit of measurement within the RDoC matrix that is calculated with subtraction-based difference scores. Future work should build upon this example and determine whether using residual difference scores and interaction terms aid in the interpretation of other measures in the RDoC matrix (e.g., utilizing residual scores to calculate fear potentiated startle).

One limitation to the current study is that a single paradigm and individual difference measure was utilized to illustrate a more general point regarding difference scores. Future work should explore these approaches in different paradigms, utilizing different psychophysiological measures, and in relation to other individual difference variables. Additionally, these analyses should be examined in relation to dimensional measures. As the use of difference scores is a more ubiquitous problem in fMRI studies, it is especially important to extend these findings to that domain. Furthermore, we hope that the current study might spur alternative analytical approaches related to difference scores in future studies.

A goal of the current investigation was to elucidate common, domain-general statistical properties of difference score calculations. We illustrated that a regression-based approach provided us with difference scores that captured unique measures of each condition, as well as demonstrating that the primary association (i.e., anxiety/ERN) was contingent on the range of the "baseline" condition (i.e., the CRN). Future studies involving two or more conditions to study individual differences should consider utilizing a regression-based approach that includes interaction terms to improve specificity and interpretability.

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