Sex moderates the association between symptoms of anxiety, but not obsessive compulsive disorder, and error-monitoring brain activity: A meta-analytic review

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Abstract

Sex differences in cognition and emotion are particularly active areas of research. Much of this work, however, focuses on mean-level differences between the sexes on cognitive and/or emotional variables in isolation. In this article, we are primarily concerned with how sex affects associations between cognition and emotion, or cognition-emotion interactions. Specifically, the purpose of this paper is to shed light on a gap in our understanding of how sex affects the relationship between error monitoring, a core component of cognitive control, and anxiety. Using meta-analysis, we show that the relationship between symptoms of anxiety and a neurophysiological marker of error monitoring—the error-related negativity (ERN)—is significantly greater in women than men such that women, but not men, with higher levels of anxiety show a larger ERN. This sex difference held true across studies of anxiety-specific symptoms but not studies of obsessive-compulsive symptoms. These findings underscore the need to consider sex in studies of anxiety and the ERN as well as support growing evidence indicating that obsessive-compulsive problems are distinguishable from other anxiety-specific problems across multiple levels of analysis. Overall, we conclude that ignoring sex in studies of cognition-emotion interactions is unacceptable. Rather, future research that continues to tackle questions related to sex differences in associations between cognition and emotion will more likely lead to advancements in basic and applied sciences of relevance to health and human behavior.

Descriptors: Sex differences, Anxiety, Obsessive-compulsive, Error-related negativity, ERN

The study of sex and gender differences spans a number of areas of psychology and neuroscience. Sex differences in cognition and emotion are particularly active areas of research (Bangasser & Valentino, 2014; Cahill, 2006, 2012, 2014; Ingalhalikar et al., 2014; Shansky & Lipps, 2013). Much of this work, however, focuses on mean-level differences between the sexes on cognitive and/or emotional variables in isolation. Although such work is important in its own right, what is lacking is research speaking to sex as a moderator of the interplay between cognition and emotion, or cognition-emotion interactions. Cognition-emotion interactions reveal important functional links demonstrating how cognition is involved in emotion and vice versa. In this article, we are therefore primarily concerned with how sex affects associations between cognition and emotion. Specifically, the purpose of this paper is to shed light on a gap in our understanding of how sex affects the relationship between error monitoring, a core component of cognitive control, and anxiety. Although significant attention has been paid to the relationship between error monitoring and anxiety, very little has been paid to sex as a potentially important contributing factor. We recently published the first paper testing for a sex difference in the relationship between anxiety and error monitoring brain activity, and showed that anxiety is related to exaggerated error-related brain signaling in female but not male undergraduates (Moser, Taylor, & Moser, 2012). We argue that such findings have significant implications for psychophysicists and individual differences researchers alike. For psychophysicists, such a sex-linked relationship can help identify the group for which the mechanism will prove most informative and refine the functional significance of a particular psychophysiological marker. For individual differences researchers, identifying such sex-linked relationships can help clarify the role of particular neural mechanisms involved in anxiety, constrain
the groups for which such relationships will be important to understand, and point to the possibility of developing assessments and interventions that are tailored to an individual’s sex.

In this paper, we use meta-analysis to further examine the potential moderating effect of sex on the relationship between anxiety and error-monitoring brain activity. Specifically, we review research on the relationship between the error-related negativity (ERN), an ERP reflecting error-monitoring processes such as rapid error correction (for reviews, see Gehring, Liu, Orr, & Carp, 2012; Yeung & Summerfield, 2012), and anxiety-related traits and disorders.

Anxiety and Its Association with the ERN

The ERN is elicited at frontocentral recording sites within 100 ms of an erroneous response (for a review, see Gehring et al., 2012). Its neural source lies, in large part, in the dorsal region of the anterior cingulate cortex (dACC)/midcingulate cortex. Additional sources of the ERN appear to be located in a distributed network including prefrontal cortex and supplementary motor areas (Gehring et al., 2012).

Although the exact functional significance of the ERN is debated, most would agree that it reflects processes involved in the adaptive regulation of behavior and cognitive control. Some have posited that the ERN indexes conflict between the intended correct response and the actual erroneous response (Yeung, Botvinick, & Cohen, 2004). Others suggest that it reflects a reinforcement learning signal indicating that the outcome—that is, the error—is worse than expected, and subsequent adjustments should be made to optimize performance (Holroyd & Coles, 2002). Recent studies further suggest that the ERN is involved in suppressing the error to give way to correcting behavior (Hochman, Orr, & Gehring, 2014; Hochman, Validya, & Fellows, 2014). Attempts at integrating multiple perspectives have also been made (e.g., Holroyd & Yeung, 2012). Nonetheless, the ERN can generally be considered a robust marker of error-monitoring processes aimed at optimizing correct responding and learning.

Modulation of the ERN by anxiety-related problems was first noted by Gehring, Himle, and Nisenson (2000), who found an enlarged ERN in obsessive-compulsive disorder (OCD) patients. OCD is characterized by unwanted and distressing thoughts (i.e., obsessions) and repetitive mental or physical behaviors (i.e., compulsions) aimed at neutralizing the distress associated with obsessions (American Psychiatric Association; APA, 2013). The dozens of studies that followed replicated these findings in OCD patients as well as extended them to new populations and anxiety-related constructs, including generalized anxiety disorder (GAD) patients and worried and trait-anxious college students (for reviews, see Olvet & Hajcak, 2008; Moser, Moran, Schroder, Donnellan, & Yeung, 2013). In fact, the ERN is one of the most robust and replicated neural markers of anxiety-related symptoms. A recent meta-analysis by our group quantified this robust association across 37 existing studies, showing that anxiety, broadly defined, demonstrates a small-to-medium relationship with enlarged ERN amplitudes (Moser et al., 2013).

The Potential Role of Sex in the Relationship Between Anxiety and the ERN

Despite the robust relationship between anxiety-related problems and the ERN, little research has examined how demographic factors affect it. Indeed, we are the only research group to our knowledge to address this issue by showing that the anxiety-ERN relationship is larger in women than men (Moser et al., 2012). The lack of attention to sex is particularly surprising to us given that anxiety-related traits and disorders show a female preponderance (Kessler et al., 2012; Kroenke, Spitzer, Williams, Monahan, & Lowe, 2007; Stavosky & Borkovec, 1988). Moreover, women suffer greater burden associated with anxiety such as longer course, higher rates of comorbidity, and greater use of healthcare services (Baxter, Vos, Scott, Ferrari, & Whiteford, 2014; McLean, Asnaani, Litz, & Hofmann, 2011). Thus, anxiety is not only more prevalent in women, but also more disabling.

Although female preponderance relative to males can be seen across most anxiety problems (Kessler et al., 2012; McLean et al., 2011), OCD does not tend to show this sex difference (see Abromowitz, Taylor, & McKay, 2009, and Altemus, Sarvaiya, & Epperson, 2014, for reviews). In fact, evidence suggests that boys are more likely to suffer from OCD than girls in childhood (Geller, 2006). What is more, a corpus of phenomenological and behavioral research suggests that OCD is distinguishable from other anxiety-related problems (for reviews, see Ameringen, Patterson, & Simpson, 2014; Goodman, Grice, Lapidus, & Coffey, 2014). OCD is, indeed, now a part of a separate section in the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013); however, OCD demonstrates significant links with other anxiety disorders and is generally conceptualized as an anxiety-related problem (Goodman et al., 2014). Given the number of observed differences between OCD and other anxiety-related problems, these findings point to the interesting possibility that the robust OCD-ERN relationship may reflect a different interplay than that of the relationship between other anxiety-related problems and enlarged ERN. To reflect the distinctions between OCD and other anxiety problems, we use terms such as anxiety and anxiety-specific problems to refer to phenomena that are specific to anxiety but not necessarily OCD. We use the blanket term anxiety-related problems to refer to all anxiety, including OCD.

Sex differences have also been noted in the amplitude of the ERN and ACC activation, the primary neural source of the ERN, although findings have been mixed. Specifically, Larson, South, and Clayson (2011) found an enlarged ERN in adult males compared to females. We did not replicate this finding in our study (Moran et al., 2012), however. Previously, Davies, Segalowitz, and Gavrin (2004) demonstrated sex differences in the developmental trajectory of the amplitude of the ERN, such that a robust ERN emerged in females around pubertal age (13–14 years) but not until early adulthood (18 years) in males. Functional neuroimaging studies likewise reveal discrepant findings: one study found increased ACC activity during conflict monitoring in females (Christakou et al., 2009), whereas another found increased ACC activity during a stop-signal task in males (Li, Huang, Constable, & Sinha, 2006). Although inconsistent, these studies highlight the importance of taking sex differences into account in ERN and ACC-related error-monitoring research.

The Current Study

To address gaps in our knowledge concerning the role of sex in the relationship between anxiety and error monitoring, the aim of the current study was to use meta-analysis to test for a possible sex difference in the association between anxiety-related problems and the ERN. Specifically, we tested whether sex moderates the association between anxiety-specific symptoms and the ERN and the association between OCD symptoms and ERN amplitude.
separately. Our rationale for separating OCD from anxiety-specific symptoms is threefold. First, OCD is the only anxiety disorder that does not show a female preponderance (Altemus et al., 2014). Second, OCD is separable from other anxiety problems across phenomenological, behavioral, and biological data (Ameringen et al., 2014). Third, our study, which showed a stronger relationship between anxiety and ERN amplitude in women than men, focused on worry symptoms (Moran et al., 2012). Thus, it is unclear whether this sex difference would generalize to OCD symptoms. For these reasons, we analyzed OCD symptoms separately.

Method

The guidelines suggested by PRISMA (http://www.prisma-statement.org/) were followed in the conduct of this meta-analysis. Studies were identified via a search of MEDLINE-PubMed and Google Scholar databases using the terms anxiety, OCD, GAD, obsessive-compulsive, generalized anxiety, worry, action monitoring, performance monitoring, conflict monitoring, error-related negativity, Ne, and ERN. Additional articles were identified by systematically searching the reference sections of all obtained articles. The following criteria were used to screen studies for inclusion (see also Figure 1):

- a. The study reported on the association between the ERN and a measure of anxiety.
- b. Due to inconsistencies in the developmental literature and potential influences of changes in gonadal hormones across the pubertal transition (Meyer, Weinberg, Klein, & Hajcak, 2012; Meyer et al., 2013), only studies that examined adult samples (i.e., 18 years or older) were included.
- c. The study reported on the response-locked ERN elicited during nonaffective conflict tasks such as the flanker task, the Stroop, and the go/no-go.
- d. Finally, as Moran et al. (2012) was the only study to report effects separately for men and women, the corresponding author of each study was contacted via e-mail in order to obtain the necessary effects. Only studies for which the necessary effects could be obtained were included in the analysis.

Additionally, we included unpublished data collected—using standard ERN elicitation methods and ERP recording procedures—by one of the authors (MJL; see Larson, Clawson, Clayson, & Baldwin, 2013, for description of participants and procedures). These criteria resulted in 37 samples drawn from 19 published and unpublished studies, including one study that reported on two samples (Endrass, Riesel, Kathmann, & Buhlmann, 2014). Sixteen studies—including the one study that reported on two samples—reported on both women and men, totaling 34 (17 women samples and 17 men samples) of the 37 included samples. The remaining three samples came from two studies that reported on only women and one study that reported on only men. Together, these 37 (19 women and 18 men) samples were comprised of 1,460 participants.

A list and description of studies is presented in Table 1. As in our previous meta-analysis (Moser et al., 2013), we included a variety of sample types including college students, community volunteers, and patients to increase the precision of our estimates and evaluate the generality of the effect across populations (Borenstein, Hedges, Higgins, & Rothstein, 2009). To demarcate sample type, we labeled college student and volunteer studies “Subclinical” and patient studies with the disorder name examined in the particular paper. Figure 1 and Table 1 show, however, that we were only able to obtain findings separated by sex for a subset of studies reported in our previous meta-analysis (Moser et al., 2013). Specifically, 70% of the studies in the current meta-analysis were included in our previous analysis, 10% were not included in our previous meta-analysis, 15% had not been published when our previous meta-analysis was underway, and 5% were unpublished data that were not available to us at the time of our previous meta-analysis. Finally, we note that the research question addressed in the present...
study concerning sex is different than the research question addressed in our previous meta-analysis (Moser et al., 2013), and thus the data were analyzed in a different manner here.

Results

Analytic Procedures

The focal effect size of the current study was Cohen’s $d$—that is, the mean difference between anxiety-related groups on ERN standardized by their pooled standard deviation. For studies reporting on differences between anxiety-related groups on ERN amplitude, Cohen’s $d$ was computed directly from the means and standard deviations; otherwise, Cohen’s $d$ was computed using the test statistic. For studies reporting correlations between anxiety-related symptoms and ERN amplitude, Cohen’s $d$ was computed as $\sqrt{r^2}$.

For all analyses, a negative Cohen’s $d$ value indicates a larger ERN in anxious individuals, whereas a positive value indicates a larger ERN in low-anxious individuals. Moderation by sex was assessed with the $Q$ statistic. $Q$ measures the degree of heterogeneity between effect sizes and follows a $\chi^2$ distribution with degrees of freedom equal to the number of groups being compared minus 1.

Given that the effect sizes were somewhat heterogeneous ($I^2 = 26.60$; however, $Q(36) = 49.05, p = .07$) and that random effects models are more appropriate in such cases (Bakermans-Kranenburg, van IJzendoorn, & Juffer, 2003; Borenstein et al., 2009), effect sizes were combined and compared using random effects models. All analyses were conducted using Comprehensive Meta-Analysis software, version 2 (Borenstein, Hedges, Higgins, & Rothstein, 2005; Biostat, Englewood, NJ).

Overall Results

Individual effect sizes are depicted in Figure 2: summary effects can be found in Table 2. Across all samples, the combined effect size relating anxiety to the ERN was significant ($d = −0.361, k = 37, N = 1,460, p < .001, 95% CI: −0.496; −0.225$). The difference between the combined effect sizes for OC symptoms and anxiety symptoms was significant, $Q(1) = 13.54, p < .001$. However, both OC symptoms ($d = −0.638, k = 14, N = 455, p < .001, 95% CI: −0.838; −0.438$) and anxiety symptoms ($d = −0.209, k = 23, N = 1,005, p = .005, 95% CI: −0.370; −0.049$) were related to a larger ERN.

Moderation by Sex

With respect to OC symptoms, effect sizes showed no heterogeneity at all ($I^2 = 0$) and thus were not moderated by participant sex, $Q(1) = 0.34, p = .56$. A larger ERN was observed in both male ($d = −0.703, k = 7, N = 202, p < .001, 95% CI: −0.999; −0.406$) and female ($d = −0.584, k = 7, N = 253, p < .001, 95% CI: −0.852; −0.316$) OC participants relative to controls.

With respect to anxiety-specific symptoms, however, effect sizes were moderately heterogeneous ($I^2 = 24.92$) and differed significantly between male and female participants, $Q(1) = 9.63, p = .002$. Although anxiety-specific symptoms were associated with a larger ERN for women ($d = −0.362, k = 12, N = 594, p < .001, 95% CI: −0.533; −0.190$), they were nonsignificantly associated with a smaller ERN for men ($d = 0.060, k = 11, N = 411, p = .57, 95% CI: −0.144; 0.264$). If we remove Rabinaik et al. (2013) because it is the only study of posttraumatic stress disorder (PTSD)—a trauma- and stress-related disorder in DSM-5 but also characterized by anxiety symptoms (APA, 2013)—and includes only males, our findings are unchanged. Effect sizes for samples of anxious men are still nonsignificant ($d = 0.062, k = 10, N = 379, p = .57, 95% CI: −0.15; 0.274$) and are smaller than those for anxious women, $Q(1) = 9.27, p = .002$. Likewise, if we remove Moran et al. (2012) because it was our initial study demonstrating the sex difference in the anxiety-ERN relationship, the same pattern of results was observed. Anxiety-related symptoms predicted a larger ERN for women ($d = −3.32, p = .001, k = 11$) but not for men ($d = 0.04, p = .74, k = 10$), and this difference was significant, $Q(1) = 5.92, p = .015$. Finally, if we just examine

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Task</th>
<th>Measure</th>
<th>Type</th>
<th>M:F</th>
</tr>
</thead>
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<tr>
<td>Aarts &amp; Pourtois, 2010</td>
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<td>Go/NoGo</td>
<td>STAI-T</td>
<td>Anx</td>
<td>4:2</td>
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<td>Flankers</td>
<td>OCI</td>
<td>OC</td>
<td>21:30</td>
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<td>Flankers</td>
<td>SCID</td>
<td>OC</td>
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<tr>
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<td>SAD</td>
<td>Flankers</td>
<td>SCID</td>
<td>Anx</td>
<td>14:34</td>
</tr>
<tr>
<td>Endrass et al., 2008</td>
<td>OCD</td>
<td>Flankers</td>
<td>SCID</td>
<td>OC</td>
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<td>STAI-T</td>
<td>Anx</td>
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<td>STAI-T</td>
<td>Anx</td>
<td>38:51</td>
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<td>Subclinical</td>
<td>Flankers</td>
<td>STAI-T</td>
<td>Anx</td>
<td>98:100</td>
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<td>Larson, unpublished Sample 1</td>
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<td>Flankers</td>
<td>MINI</td>
<td>Anx</td>
<td>16:54</td>
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<td>Larson, unpublished Sample 2</td>
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<td>Stoop</td>
<td>PSWQ</td>
<td>Anx</td>
<td>96:89</td>
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<td>Moran et al., 2012</td>
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<td>PSWQ</td>
<td>Anx</td>
<td>70:79</td>
</tr>
<tr>
<td>Olvet &amp; Hajcak, 2009</td>
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<td>Flankers</td>
<td>DASS</td>
<td>Anx</td>
<td>18:11</td>
</tr>
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<td>Rabinaik et al., 2013</td>
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<td>Flankers</td>
<td>SCID</td>
<td>Anx</td>
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<td>Riesel et al., 2011</td>
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<td>Flankers</td>
<td>SCID</td>
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<td>Weinberg et al., 2010</td>
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<td>Flankers</td>
<td>SCID</td>
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<td>Weinberg et al., 2012</td>
<td>GAD</td>
<td>Flankers</td>
<td>SCID</td>
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<td>−62</td>
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<tr>
<td>Zambrano-Vasquez &amp; Allen, 2014</td>
<td>Subclinical</td>
<td>Flankers</td>
<td>PSWQ</td>
<td>Anx</td>
<td>−33</td>
</tr>
</tbody>
</table>

Note. Population acronyms: GAD = generalized anxiety disorder; OCD = obsessive compulsive disorder; PTSD = posttraumatic stress disorder; SAD = social anxiety disorder. Anxiety measure acronyms: DASS = Depression Anxiety Stress Scale; MINI = Mini-International Psychiatric interview; OCI = Obsessive-Compulsive Inventory; PSWQ = Penn State Worry Questionnaire; SCID = Structured Clinical Interview for DSM Disorders; STAI-T = State-Trait Anxiety Inventory-Trait. Type of measure: Anx = anxiety-specific; OC = obsessive-compulsive.
studies focused on worry-related problems (i.e., worry and GAD), as we did in our previous sex difference study (Moran et al., 2012), the results remain the same. The worry-ERN relationship is significant for women ($d = 0.398, k = 6, N = 347, p < .001, 95\% \text{ CI}: -0.619; -0.177$) but not for men ($d = 0.138, k = 4, N = 193, p = .35, 95\% \text{ CI}: -0.153; 0.429$). These effect sizes between women and men were significantly different, $Q(1) = 8.26, p = .004$.

**Discussion**

The aim of the present study was to evaluate the possible moderating effect of sex on the relationship between anxiety-related problems and the ERN. Results from the meta-analysis indicated that sex moderates the association between anxiety-specific symptoms and ERN but not the association between OCD symptoms and ERN. Specifically, anxiety was associated with an enlarged ERN in women but not in men. In contrast, OC symptoms were associated with an enlarged ERN in both women and men.

The current findings across anxiety studies extend our previous results in college students (Moran et al., 2012) by further supporting the role of sex as an important factor in the relationship between anxiety and the ERN. The relationship between OCD and ERN was not moderated by sex, however, providing additional evidence for sex differences in anxiety-related processes.

**Table 2. Results of the Meta-Analysis**

<table>
<thead>
<tr>
<th>Sample</th>
<th>$d$</th>
<th>$k$</th>
<th>$N$</th>
<th>$p$</th>
<th>95% CI</th>
</tr>
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<tr>
<td>All samples</td>
<td>$-0.361$</td>
<td>37</td>
<td>1,460</td>
<td>&lt; .001</td>
<td>$-0.496; -0.225$</td>
</tr>
<tr>
<td>OC symptoms</td>
<td>$-0.637$</td>
<td>14</td>
<td>455</td>
<td>&lt; .001</td>
<td>$-0.836; -0.439$</td>
</tr>
<tr>
<td>Anxiety symptoms</td>
<td>$-0.209$</td>
<td>23</td>
<td>1,005</td>
<td>.005</td>
<td>$-0.370; -0.049$</td>
</tr>
<tr>
<td>OC–men</td>
<td>$-0.703$</td>
<td>7</td>
<td>202</td>
<td>&lt; .001</td>
<td>$-0.999; -0.406$</td>
</tr>
<tr>
<td>OC–women</td>
<td>$-0.584$</td>
<td>7</td>
<td>253</td>
<td>&lt; .001</td>
<td>$-0.852; -0.316$</td>
</tr>
<tr>
<td>Anxiety–men</td>
<td>$.060$</td>
<td>11</td>
<td>411</td>
<td>.57</td>
<td>$-0.144; 0.264$</td>
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<tr>
<td>Anxiety–women</td>
<td>$-0.362$</td>
<td>12</td>
<td>594</td>
<td>&lt; .001</td>
<td>$-0.533; -0.190$</td>
</tr>
</tbody>
</table>

OC and anxiety symptoms differ significantly, $Q(1) = 13.54, p < .001$.

Men and women did not differ for OC symptoms, $Q(1) = 0.34, p = .56$.

Men and women differed significantly for anxiety symptoms, $Q(1) = 9.63, p = .002$. 

**Figure 2.** Forest plot depicting effect sizes for each study and for men and women as a function of sample type. Error bars represent the 95\% confidence interval.
evidence indicating that OCD is distinguishable from anxiety-specific problems (Ameringen et al., 2014). It is also noteworthy that, overall, OCD demonstrated a stronger relationship with the ERN than other forms of anxiety. Together, the current findings suggest that the ERN reflects a different process and/or is influenced by different mechanisms in OCD compared to other forms of anxiety.

Thus, in drawing attention to sex differences in the relationship between anxiety and error monitoring, we revealed that the ERN represents a reliable correlate of anxiety in women, but not in men. There are a number of implications that follow from this result to which we now turn.

Practical Implications

First, the current findings suggest that the ERN may only be a useful marker of anxiety in women, but not men. Although future research should continue to evaluate the sex difference in the anxiety-ERN relationship, our findings suggest that studies could primarily focus on female-only samples in future investigations examining non-OCD type anxiety. Ideally, all future studies of the anxiety-ERN relationship would be adequately powered to test sex effects; however, given practical constraints of time, money, and other resources, smaller-scale studies should consider selecting only female participants.

Without attending to sex, studies might underestimate effects. For example, a researcher who conducts a small-scale study with an equal (or, likely, unequal) number of men and women might underestimate an effect if a small-to-moderate effect exists in one group and a zero or opposite effect exists in the other. Similarly, a research group may underestimate an effect by only including men. Indeed, Rabinak et al. (2013) recently examined the relationship between PTSD and ERN in male veterans only and concluded that “PTSD is not associated with an abnormal ERN response” (from Abstract). Without a group of female veterans, this conclusion seems premature. Given the results of the current analysis, it is possible that PTSD is associated with an enlarged ERN in women, but not in men.

Mechanistic Implications

Ignoring sex in psychophysiological studies assumes that mechanisms associated with anxiety are the same across all anxious individuals and function in the same ways—hopefully, an assumption that is challenged by the results of our meta-analysis. Anxiety was only related to an enlarged ERN in women, suggesting that female-predominant/typical mechanisms may be at play. For instance, we recently suggested that verbal mechanisms might play an important role in the anxiety-ERN relationship in females (Lin, Moran, Schroder, & Moser, in press). Two sets of findings were the primary motivation for investigating this possibility: (1) that the worry-ERN relationship was much larger in women than men (Moran et al., 2012), and (2) that females tend to use verbally mediated semantic learning and problem-solving strategies (Beilock, Rydell, & McConnell, 2007; Kramer, Delis, & Daniel, 1988; Kramer, Delis, Kaplan, O’Donnell, & Priftlera, 1997).

Indeed, Beilock and colleagues have conducted several studies examining the role of verbal mechanisms in explaining the impact of anxiety on female academic performance. Drawing on stereotype threat, expertise, and anxiety research, Beilock and colleagues have shown that the deleterious effects of verbal worries in trait-anxious female students impairs their cognitive performance more so than their male counterparts—especially in females with high working memory capacity who tend to use complex verbal strategies (Beilock, 2010; Ramirez & Beilock, 2011). Together, research suggests that the ERN likewise reflects the particularly impairing effects of verbal worry on cognitive functioning in women. Specifically, consistent utilization of verbal processes during problem situations may promote subvocal articulation as a general response to threat or uncertainty. The sex difference in the worry-ERN relationship may therefore reflect the greater interference of subvocal rehearsal in women relative to equally worried men during both engagement and monitoring of task performance.

Another important possibility is that the sex difference in the anxiety-ERN relationship reflects influences of gonadal hormones. Ovarian hormones, in particular, predominate in females, may be involved in anxiety and mood symptoms (Altemus, Dhabhar, & Yang, 2006; Hyde, Mezulis, & Abramson, 2008), and are potent organizers/ regulators of frontal brain regions involved in cognitive control (for a review, see Cahill, 2006). Researchers in other areas of anxiety have already begun examining the role of ovarian hormones in studies of fear conditioning in PTSD (e.g., Glover et al., 2012). Of particular relevance to the current paper, recent animal work suggests estradiol may be primarily responsible for anxiety-related cognitive dysfunction (for a review, see Shansky & Lips, 2013). Moreover, estradiol is highly concentrated in regions that give rise to the ERN and modulates the primary neurotransmitter involved in the generation of the ERN (i.e., dopamine; Cahill, 2006). Although less well understood, progesterone’s role in anxiety (Toufexis, Myers, & Davis, 2006) and emotion processing (Van Wingen, Ossewaarde, Bäckström, Hermans, & Fernandez, 2011) suggest that it may also be important to consider in the anxiety-ERN relationship.

Given that the current findings indicate that enlarged ERN is a reliable marker of anxiety in women, do we know anything about what else might be a reliable marker of anxiety in men? Indeed, we do. In fact, it could be argued that we know considerably more about the mechanisms involved in male anxiety than female anxiety because of the extensive animal studies of anxiety that have predominantly used males (Cahill, 2012; Cover, Maeng, Lebron-Milad, & Milad, 2014). For example, studies of fear conditioning and extinction, mechanisms considered to play major roles in anxiety, have predominantly relied on animal paradigms conducted in males (Cover et al., 2014). Although the findings have been mixed in humans, Shvil et al. (2014) recently showed that male PTSD patients, but not female PTSD patients, demonstrated poorer extinction recall. Male, but not female, PTSD patients also showed greater activation of dACC during extinction recall. Thus, enhanced ACC activity during extinction recall might be a promising marker of anxiety in men. Finally, we reiterate that the results of the current analysis do, indeed, indicate that the ERN is a reliable marker of OCD in men.

Future Directions

Having provided evidence for a sex difference in the relationship between anxiety and enlarged ERN, there are a number of exciting avenues for future research we are taking up and hope that others will as well. First, the possibility that verbal mechanisms might help explain the anxiety-ERN relationship in women has prompted us to think about interventions aimed at relieving the significant drain of verbal worries on cognitive resources in women. For instance, we recently showed that a brief expressive writing intervention significantly reduces the ERN in chronically worried...
female undergraduates (Schröder, Moran, & Moser, 2013). The use of expressive writing was motivated by findings indicating that expressive writing has specific impact on decreasing the interference of verbal worries on performance and may do so via the “offloading” of worry from verbal working memory (Kellogg, Mertz, & Morgan, 2010; Klein & Boals, 2001; Park, Ramirez, & Beilock, 2014; Ramirez & Beilock, 2011). Given these promising findings, additional studies should be undertaken to further clarify the associations between worry, verbal processes, ERN, and working memory in women.

Investigating the role of gonadal hormones will also be important. This possibility could be examined in a number of ways. First, the anxiety-ERN relationship could be examined across the menstrual cycle. The menstrual cycle offers a naturally occurring quasi experimental paradigm to begin investigating the role of ovarian hormones in the association between anxiety and ERN, as the menstrual cycle is characterized by predictable fluctuations in ovarian hormone (i.e., estradiol and progesterone) levels. Direct measurement of hormones will also be important, as menstrual cycle effects only provide a proxy for how fluctuations in actual hormone levels might contribute to the anxiety-ERN relationship. Finally, studies of women on versus off hormonal contraceptives will provide yet another way to interrogate the role of gonadal hormones, as hormonal contraceptives alter the naturally occurring fluctuations in hormones across the menstrual cycle (Fleischman, Navarrete, & Fessler, 2010; Mareckova et al., 2014). Research using all of these paradigms has begun to emerge in the study of fear extinction in healthy individuals and those diagnosed with PTSD (Glover et al., 2012; Graham & Milad, 2013) and thus provides a model for how to proceed in studies of the association between anxiety and enlarged ERN. We have therefore begun employing such paradigms in recent studies.

Clinically, the current findings might help form the foundation of the development of individualized assessments and treatments that could maximize outcomes for anxious individuals (Bangasser & Valentino, 2012). The results of the current meta-analysis suggest that the ERN is most useful as a marker of anxiety in women, but is useful as a marker of OCD in both women and men. Early detection, treatment, and etiological studies should then consider the current findings when deciding on recruitment strategies. Hopefully, targeting the relevant sex would result in better early detection, treatment outcomes, and understanding of causal mechanisms.

As additional evidence amasses, we will also be able to evaluate sex differences in the anxiety-ERN and OCD-ERN relationship with respect to other potential moderator variables such as type of task used to elicit the ERN and anxiety type (e.g., worry vs. trait-anxiety, as we have done before in Moser et al., 2013). Examining such moderators in the current meta-analysis was difficult given the limited amount of data we were able to attain separated by sex. Collapsing across tasks and anxiety measures was important for the current analysis to provide the most precise estimate with the most relevance across different populations, but because of the limited data available, we were not able to further evaluate the role of other moderators of potential significance to the anxiety-ERN and OCD-ERN relationships.

Finally, although not available for the current analysis, future research should also examine whether there are sex differences in the relationship between anxiety-related problems and behavior. We reported no relationship between anxiety and behavior in our previous meta-analysis (Moser et al., 2013), nor did we find a sex difference in the relationship between worry and behavior in our college student study (Moran et al., 2012). However, larger-scale examinations of potential sex differences in the anxiety-behavior relationship should be conducted to better understand the functional link between anxiety-related problems and enlarged ERN.

Conclusion

Sex is an important explanatory variable in research on cognition and emotion, but much of the work in this field has largely focused on mean-level differences rather than sex differences in associations between cognition and emotion. Focusing on these sex differences can shed light on how sex affects mechanistic relationships. Findings from our meta-analysis demonstrate the importance of examining sex as a moderator by showing that the relationship between anxiety and enlarged ERN—one of the most well-documented neural markers of anxiety—is much larger in women than men. Ignoring sex in future studies of anxiety and the ERN is therefore unacceptable because it precludes our ability to better understand the precise role of the ERN in the development, maintenance, and treatment of anxiety and related problems (e.g., OCD) across the sexes. Indeed, the National Institutes of Health are making studying sex differences a priority and mandating sex and gender inclusion plans for clinical and animal research (Clayton & Collins, 2014). Thus, for both basic and translational reasons, it is extremely important for ERN researchers, psychophysioligists, and allied scientists to pay attention to sex.

References

*References included in the meta-analysis


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