Abstract

Although cognitive-behavioral psychotherapy (CBT) and pharmacotherapy are evidence-based treatments for pediatric anxiety, many youth with anxiety disorders fail to respond to these treatments. Given limitations of clinical measures in predicting treatment response, identifying neural predictors is timely. In this study, 35 anxious youth (ages 7-19 years) completed an emotional face-matching task during which the late positive potential (LPP), an event-related potential (ERP) component that indexes sustained attention towards emotional stimuli, was measured. Following the ERP measurement, youth received CBT or selective serotonin reuptake inhibitor (SSRI) treatment, and the LPP was examined as a predictor of treatment response. Findings indicated that, accounting for pre-treatment anxiety severity, neural reactivity to emotional faces predicted anxiety severity post- CBT and SSRI treatment such that enhanced electrocortical response to angry faces was associated with better treatment response. An enhanced LPP to angry faces may predict treatment response insofar as it may reflect greater emotion dysregulation or less avoidance and/or enhanced engagement with environmental stimuli in general, including with treatment.

Keywords: anxiety; event-related potential (ERP); late positive potential (LPP); treatment response

Neural Reactivity to Angry Faces Predicts Treatment Response in Pediatric Anxiety

Anxiety disorders (ADs) are among the most prevalent psychiatric disorders in children and adolescents and are associated with psychiatric comorbidity, subjective distress, and functional impairment (Beesdo, Knappe, & Pine, 2009). To address these negative sequelae of pediatric ADs, early intervention is key. Two empirically supported treatments for pediatric ADs are cognitive-behavioral therapy (CBT; Kendall, 1994; Kendall et al., 1997) and pharmacotherapy (e.g., Birmaher et al., 2003). Yet, approximately 40-50% of youth with ADs do not respond to these monotherapies (e.g., Bridge et al., 2007; James, James, Cowdrey, Soler & Choke, 2015). Identifying which treatments work for which youth may ultimately result in better rates of treatment response. To this end, examining the utility of neural predictors is prudent, given both that differential treatment response may reflect pathophysiological heterogeneity and that clinical and demographic measures are weak predictors (see Ball, Stein, & Paulus, 2014 for review). If neural measures were validated as predictors of treatment response, their assessment may contribute to advances in personalized medicine.

Clinical and Demographic vs. Neural Predictors of Treatment Response

Research on clinical predictors of treatment response in youth with ADs is primarily focused on symptoms, demographics and environmental factors (e.g., family characteristics). For example, co-occurring social anxiety, family dysfunction, and parenting stress have been related to worse CBT response (Crawford, & Manassis, 2001; Layne, Bernstein, Egan, & Kushmer, 2003). Higher IQ has been related to better CBT and pharmacotherapy response (D'Alcante et al., 2012; Layne et al., 2003). Although in one study males responded better to CBT than females, demographic factors in general (e.g., age, gender, and socioeconomic status) are inconsistent predictors (Layne et al., 2003). In addition, these measures tend to account for a

relatively small portion of variance in treatment response (ranging from zero to 25% across studies), yet there is increasing evidence that neural measures may be more robust predictors. For example, among adults, pre-treatment anxiety severity accounts for 12% of the variance in changes in anxiety symptoms following CBT (Doehrmann et al., 2013; Whitfield-Gabrieli et al., 2016) whereas the inclusion of neuroimaging data triples (Doehrmann et al., 2013) or close to doubles (Whitfield-Gabrieli et al., 2016) the amount of variance accounted for. These findings indicate that clinical and demographic measures are relatively weak predictors of treatment response but neural measures are promising, underscoring the need for continued research on neural predictors (see Ball et al., 2014 for review; Gabrieli, Ghosh, & Whitfield-Gabrieli, 2015).

Biases in Attending/Orienting to Threat and the Development and Maintenance of Anxiety

Conceptual models of anxiety indicate biases in cognitive processes related to threat processing as key to the development and maintenance of ADs (Beck & Clark, 1997; Pine, 2007). Specifically, ADs are associated with biases in attending/orienting, appraisal and learning (Pine, 2007) and these biases manifest in the elicitation of threat responses in contexts where these responses are inappropriate or unnecessary. The association between ADs and biases in attending, appraisal, and learning is relevant across development, and early-appearing biases in attending likely predict later biases in appraisal and learning (Pine, 2007). Nonetheless, although these processes show heterotypic continuity (Pine, 2007), there is also evidence for maturational differences in attention towards threat. For example, over development, youth are able to apply increasingly complex schemes to more diverse types of threat, indicating an enhanced understanding of threat, which likely reflects developmental changes in underlying neural mechanisms (Pine, 2007).

The literature on developmental changes in the neural bases of anxiety is limited (Blackford & Pine, 2012). Although there is some evidence that similar neural circuits are involved in anxiety across development, there are also age-related changes in the interaction among those structures. For example, in response to fearful faces, children with generalized anxiety and panic disorder exhibit enhanced amygdala activation (Thomas et al., 2001) and so do adolescents with subclinical anxiety (Killgore & Yurgelun-Todd, 2005). On the other hand, developmental changes have been observed in interaction between the amygdala and regions associated with appraisal and emotion regulation and these patterns differ between youth with and without anxiety in that in the former group age is positively related to connectivity whereas in the latter group age is negatively related to connectivity (Kujawa et al., 2016). Nevertheless, although there is indication for age-related changes in both behavioral indices and neural correlates of processes involved in the development and maintenance of ADs, the nature and time course of such changes remain largely unclear (Pine, 2007).

Neural Activation during Attending/Orienting as a Potential Predictor of Treatment Response

Given the relevance of attending to threat in ADs, neural activation in brain areas involved in early processing of emotional stimuli may be a useful predictor of treatment response. Indeed, the findings of two recent studies indicate that, in response to threatening stimuli, enhanced pre-treatment activation in higher-order visual regions is associated with CBT response among adults with social anxiety disorder (SAD). Doehrmann et al. (2013) found that, controlling for pre-treatment symptom severity, enhanced activation in the dorsal and ventral occipitotemporal cortex to angry faces predicted better CBT response. Similarly, Klumpp, Fitzgerald, and Phan (2013) found that, controlling for pre-treatment symptom severity,

enhanced activation in higher-order visual (superior and middle temporal gyrus) areas to angry and fearful faces predicted better CBT response. Although certainly promising, the literature on neural predictors of treatment response is predominantly comprised of studies using functional magnetic resonance imaging (fMRI) and conducted with adults (Ball et al., 2014), underscoring the need for additional research on neural predictors, including with methods that are economically and feasibly obtained and with youth (Ball et al., 2014).

ERP Measures of Attending to Threat across Development

Regarding methods, event-related potentials (ERP) allow for measuring neural activation related to attention towards affective stimuli and, relative to fMRI, are more economical and feasible to assess in youth, thus potentially more applicable to clinical settings. Of interest to the present research is the late positive potential (LPP), a sustained positivity in the ERP wave to affective stimuli. As such, the LPP reflects attention towards and elaborative processing of emotionally salient stimuli and activation of motivational systems (Cuthbert et al., 2000; Hajcak, Weinberg, MacNamara, & Foti, 2011; Schupp, Flaisch, Stockburger, & Jungöfer, 2006; also see Hajcak, MacNamara, & Olvet, 2010 for review) relevant to the process of attending/orienting. Prior findings indicate the LPP is internally consistent (Moran, Jendrusina, & Moser, 2013) and can be reliably assessed across development (Kujawa, Klein, & Proudfit, 2013). Regarding its validity, data on the LPP indicate an association between attending to more arousing or emotional aspects of stimuli and an enhancement in the LPP as well as an association between the use of emotion regulation skills and an attenuation in the LPP (e.g., Hajcak & Nieuwenhuis, 2006).

Among adults with ADs, the LPP has been shown to correspond to reactivity towards threat. For example, findings indicate enhanced LPPs to spider images among adults with spider

phobia (Leutgeb et al., 2009; Michalowski et al., 2009), to faces among adults with social anxiety (Moser et al., 2008; Mühlberger et al., 2009), and to aversive images among adults with generalized anxiety disorder (GAD; MacNamara & Hajcak 2010; MacNamara, Kotov & Hajcak, 2016). Findings further indicate enhanced LPP to spider stimuli among children with spider phobia (Leutgeb et al., 2010) and to angry and fearful faces among children and adolescents with ADs relative to healthy controls (Kujawa, MacNamara, Fitzgerald, Monk, & Phan, 2015).

Regarding pediatric samples, there is a considerable paucity of research on neural predictors of treatment response in general. We know of only one study using ERPs and of only two studies using fMRI to predict treatment response in pediatric ADs. Regarding the former, the findings of Hum, Manassis, and Lewis (2013) indicate that greater P1 (reflecting attention and/or arousal) during a Go/No-go task using emotional facial expressions was associated with worse CBT response and greater N2 (reflecting cognitive control) was associated with better CBT response. Regarding the studies using fMRI, data indicated a positive association between pre-treatment amygdala activation and CBT and selective-serotonin response inhibitor (SSRI) response in youth with GAD (McClure et al., 2007), as well as a positive association between pre-treatment activation in prefrontal regions and CBT and SSRI response among children and adolescents with GAD, separation anxiety disorder, and/or SAD (Kujawa et al., 2015b). Although these data indicate there may be utility in examining neural predictors of treatment response in pediatric samples, they also highlight the need for continued research on such predictors. It is prudent for such continued research to be informed by developmental considerations for two primary reasons; first, some evidence indicates younger age is associated with better pharmaco- and psychotherapy response among youth with ADs (Ginsburg et al., 2011) and biological markers may reflect such age-related differences in treatment response.

Second, there are developmental changes in the neural systems implicated in emotion processing (Monk, 2008), further suggesting that adult neural predictors may not extend to youth.

The Present Study

Taken together, the literature indicates neural predictors may be useful indices of treatment response, but additional research is needed with methods that are clinically practical and with youth. Accordingly, our goal in the present research was to examine the association between ERPs to emotional faces, and psycho- and pharmacotherapy response in youth with ADs. Specifically, we examined whether differences in pre-treatment LPP to emotional faces (i.e., angry, fearful, and happy) predicted CBT and/or SSRI response in youth with ADs. In light of prior findings, we hypothesized that enhanced LPPs following threatening (angry and fearful) faces would be positively associated with treatment response. In the absence of prior findings on neural processing of happy faces and treatment response, our pertinent analyses were exploratory.

Method

Procedures

Youth with primary diagnoses of GAD, separation anxiety disorder, and SAD were recruited at the University of Michigan (UM) and University of Illinois at Chicago (UIC) in the context of a two-site treatment study modeled after the Child/Adolescent Anxiety Multimodal Study (CAMS; Walkup et al., 2008). Youth with cognitive or developmental disabilities, lifetime psychotic illness and current severe depression or suicidal ideation were excluded. Eligible youth at UM self-selected into CBT or SSRI (13 youth self-selected into CBT and nine self-selected into SSRI) and at UIC were randomized to CBT or SSRI with the option to switch in case of medication side effects. Psychotherapy followed a manualized CBT intervention for pediatric

anxiety; the Coping Cat (Kendall & Hedtke, 2006) for children and the C.A.T. Project (Kendall, Choudhury, Hudson, & Webb, 2002) for adolescents, which includes psychoeducation, cognitive restructuring, and exposures. CBT was delivered weekly, in 60-minute sessions (for up to 18 sessions, as clinically indicated) by master's- or doctoral-level clinicians. For pharmacotherapy, sertraline was prescribed by a child psychiatrist on a fixed-flexible schedule beginning with 12.5 or 25 mg/day and adjusted up to 200 mg/day given tolerability and treatment response for 12 sessions. ERP assessments took place pre-treatment. Clinical assessments were completed before the first treatment session and after the last treatment session.

Participants

Fifty-two youth, who had LPP, pre- and post-treatment clinical data and completed at least 10 sessions of CBT or SSRI were included in this study. Two were excluded for missing cognitive or clinical data and 13 for noisy EEG data or < 70% accuracy on the experimental task. Given that depressive symptoms were associated with a blunted LPP in this sample (Kujawa et al., 2015a), two additional youth were excluded for comorbid depression, to avoid confounding treatment response effects, leaving a final sample of 35 participants (ages 7-19 years: M = 14.06, SD = 3.56). Independent samples t-tests indicated an age difference between the youth who were excluded (M_{age} = 10.35, SD = 3.21) and the youth who were retained (M_{age} = 14.05, SD = 3.56), in that the excluded group was younger (p = .001). Youth who were excluded and youth who were retained did not significantly differ on ethnicity, race, gender, study site, treatment type, pre-treatment anxiety severity, or primary AD diagnosis (all ps > .13). Because not all youth who were excluded and who were retained had complete data on depression, post-treatment anxiety severity, IQ, or LPP variables (or behavioral performance variables), we were unable to compare youth on these indices. Of the final sample, approximately half (51.4%) were female and 57.1%

identified as Caucasian, 22.9% as Hispanic/Latino, 8.6% as Asian or Pacific Islander, 5.7% as African American, and 5.7% as biracial/multiracial.

Regarding ADs, 71.4% of the sample had current GAD, 5.7% separation anxiety disorder, and 51.4% SAD. 5.7% also had obsessive-compulsive disorder, 11.4% panic disorder, 22.9% specific phobia, 14.3% attention-deficit/hyperactivity disorder (ADHD) and 2.9% oppositional defiant disorder (ODD). 48.6% had one, 37.1% had two, 11.4% had three, and 2.9% had four current ADs.

Measures

Diagnostic interview. Clinical diagnoses were determined using the Kiddie Schedule of Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997), administered by master's- or doctoral-level clinicians (see Kujawa et al., 2015a for additional details). Prior findings indicate the K-SADS has acceptable psychometric properties including test-retest reliability (>.70) for any AD and GAD (Kaufman et al., 1997). Inter-rater reliability has also been shown to be acceptable (κ = .84; Ulloa et al., 2006 and between .80 and .90; Birmaher et al., 2009) and so has convergent, discriminant, divergent and predictive validity (Birmaher et al., 2009).

Anxiety severity. Following the CAMS (Walkup et al., 2008), anxiety severity was measured on the Pediatric Anxiety Rating Scale (PARS; Research Units on Pediatric Psychopharmacology [RUPP] Anxiety Study Group, 2002), an interviewer-rated measure of anxiety symptom severity. Interviewers rated seven dimensions of anxiety (frequency and number of symptoms, overall symptom severity, physical symptom severity, avoidance, and interference at home and outside of the home) on a 6-point scale, with the dimensions then combined to form a total score. Prior data indicate that the PARS has excellent inter-rater

reliability (ICC = .97), adequate test-retest reliability (ICC = .55), borderline internal consistency (α = .64), satisfactory convergent and discriminant validity, sensitivity to treatment effects paralleling change in other anxiety symptoms and global functioning measures (RUPP Anxiety Study Group, 2002). In the present sample, internal consistency ranged from borderline acceptable to good (α =.66 and .83 for pre- and post-treatment PARS, respectively). Of note, by their nature, measures of broad constructs tend to have lower internal consistency than measures of narrower constructs (Peters, 2014), and the α obtained in the present sample is similar to that obtained in the standardization sample (RUPP Anxiety Study Group, 2002).

Covariates. Covariates were age (given developmental changes in LPPs; MacNamara et al., 2016), depressive symptoms, and IQ (given that IQ is associated with CBT and SSRI response; e.g., D'Alcante et al., 2012). We used the Children's Depression Inventory (CDI; Kovacs, 1992) to measure depressive symptoms and the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II; Wechsler, 1999) to measure cognitive ability. In the present sample, internal consistency for the CDI was good (α =.84).

Emotional face-matching task. Pre-treatment, youth completed an emotional face-matching task (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002) that was previously used by our group to measure LPPs in youth (MacNamara et al., 2016; Kujawa et al., 2015a). Youth were presented with three images in a triangular arrangement for 3,000 msec, and selected which one of two images at the bottom of the screen matched the image at the top of the screen. In face-matching trials, an angry, fearful, or happy face was presented at the top of the screen and a different angry, fearful, or happy face as well as a neutral face were presented at the bottom of the screen. Shape-matching trials, wherein youth matched geometric shapes, were included to measure LPPs in a neutral condition. Youth completed six practice trials, followed by two blocks

with 12 trials for each condition presented in a random order within each block (24 trials per condition total). The interval between trials lasted between 1,000-3,000 msec.

ERP data collection and processing. Continuous EEG was recorded using a BioSemi (Amsterdam, Netherlands) 34-channel cap (32 channel cap plus FCz and Lz). Electrodes were placed on the left and right mastoids, and electrooculogram was recorded from four facial electrodes placed approximately 1 cm above and below the right eye and beyond the outer edge of each eye. Data were digitized at 24-bit resolution with a Least Significant Bit (LSB) value of 31.25 nV and a sampling rate of 1,024 Hz. Data were processed offline using Brain Vision Analyzer software (Brain Products, Gilching, Germany), converted to a linked mastoid reference, and filtered with high-pass and low-pass filters of 0.01 and 30 Hz, respectively. Data for correct trials were segmented beginning 200 msec before stimulus onset and continuing for the 3,000 msec stimulus duration. Eyeblinks were corrected using the method by Gratton, Coles, and Donchin (1983), and semi-automated artifact rejection procedures removed artifacts with voltage step of more than 50 μV between sample points, voltage difference of 300 μV within a trial, and maximum voltage difference of less than 0.5 μV within 100 msec intervals. Additional artifacts were removed using visual inspection.

ERPs were averaged across each condition and baseline corrected to the 200 msec prior to stimulus onset. The LPP was scored at a pooling of O1, O2, Oz, PO3, PO4, P3, P4, and Pz (Kujawa et al., 2015a). Given the relatively long stimulus duration (i.e., 3000 msec) in the current task as well as our prior findings indicating that anxiety effects on LPPs are most apparent 1,000–3,000 msec after stimulus onset (Kujawa et al., 2015a), we used the 1,000–3,000 msec window to index the LPP. Analyses were conducted on the emotional face minus shapes difference score to isolate ERPs specific to emotional face processing.

Data Analysis

Hierarchical multiple regression analyses were conducted to examine predictors (behavioral performance and LPPs) of post-treatment anxiety severity. Post-hoc analyses testing an interaction between LPP and treatment type, between LPP and primary anxiety diagnosis, and between LPP and gender on post-treatment anxiety severity were conducted for significant models. Separate models were tested for angry, fearful, and happy LPPs for the following reasons: first, individuals, including with anxiety, respond differently to angry, fearful, and happy faces as these socio-emotional signals have different salience (e.g., Adams & Kleck, 2002; Campbell et al., 2009; Coles & Heimberg, 2005; Ewbank et al., 2009; Fox, 2002; Fox, Russo, Bowles, & Dutton, 2001); second, our own as well as other groups have found associations for one expression but not the other two, depending on outcome or predictor variables of interest (e.g., Bunford et al., under review; Doehrmann et al., 2013; Klumpp et al., 2013); third, angry, fearful, and happy LPPs were highly correlated in the current sample (angry-fearful $r = .68$; $p < .001$; angry-happy $r = .64$; $p < .001$; fearful-happy $r = .41$; $p = .033$). Step 1 included all covariates of interest (age, depressive symptoms, and IQ), step 2 included pre-treatment PARS, and step 3 included the LPP variables.

Results

Participant Characteristics

In terms of clinical change pre- to post-treatment, both anxiety severity, $t(34) = 10.34$, $p < .001$, mean difference = 10.46, and depressive symptoms, $t(34) = 25.29$, $p < .001$, mean difference = 44.77, decreased pre- to post-treatment.

Treatment groups; CBT ($n = 19$) vs. SSRI ($n = 16$) did not differ in pre-treatment anxiety severity, race, or sex (ps > .41). Those in CBT exhibited less depressive symptoms, $t(33) = 2.29$,

p = .028 and were younger, $t(33) = 3.07$, p = .004. As expected, those in CBT completed more sessions than those in SSRI, $t(33) = -9.02$, $p < .001$ though treatment groups did not differ in post-treatment anxiety severity, $t(34) = .66$, p = .59, mean difference = 1.35.

Study sites did not differ in treatment type, depressive symptoms, age, race, sex, or primary diagnosis (ps > .06). Relative to UM, the UIC sample exhibited higher anxiety severity, $t(34) = -2.81$, p = .008. Thus, site was also entered into the regression models in step 1 as a covariate.

Behavioral Performance

Accuracy and reaction time (matching angry faces vs. shapes, matching fearful faces vs. shapes, and matching happy faces vs. shapes) did not predict post-treatment anxiety severity (ps > .21). Of note, accuracy on the task overall was within acceptable limits. We have previously reported on emotion effects on behavioral performance and our prior findings indicated youth exhibited greatest accuracy for matching shapes, followed by matching happy faces, fearful faces, and finally angry faces. Our prior findings further indicated longest RT for matching angry faces, followed by fearful faces, happy faces, and finally matching shapes (Kujawa et al., 2015a).

LPP to Emotional Faces

Regarding bivariate correlations, the LPP to angry faces did not correlate with pre- or post-treatment anxiety severity or depressive symptoms (ps > .06). Similarly, the LPP to fearful or happy faces did not correlate with pre- or post-treatment anxiety severity or depressive symptoms (ps > .20).

Controlling for covariates, baseline anxiety severity did not (p = .34) but LPP to angry faces did ($\Delta F = 4.81$, p = .04) predict post-treatment anxiety severity (see Table 1), such that an enhanced LPP to angry faces was associated with lower post-treatment anxiety severity (Figure

1). To illustrate these data, a median-split on post-treatment anxiety severity (residuals controlling for pre-treatment severity) was performed. Figure 2 depicts ERPs and scalp distributions for treatment responder (i.e., low post-treatment anxiety severity) and for treatment nonresponder youth (i.e., high post-treatment anxiety severity).

Post-hoc analyses testing the effects of an interaction between LPP to angry faces and treatment type, of an interaction between LPP to angry faces and primary anxiety diagnosis, and of an interaction between LPP to angry faces and gender[1] on post-treatment anxiety severity were nonsignificant (*p*s > .07).

Controlling for covariates, neither baseline anxiety severity nor LPP to fearful faces predicted post-treatment anxiety severity (*p*s > .22). Similarly, controlling for covariates, neither baseline anxiety severity nor LPP to happy faces predicted post-treatment anxiety severity (*p*s > .34).

Discussion

Our goal in this study was to examine whether a neural measure of emotional face processing (i.e., LPP) predicted CBT and SSRI response among anxious youth. An enhanced LPP to angry faces was associated with lower post-treatment anxiety severity, adjusting for baseline severity. This effect did not vary by treatment type or by primary anxiety diagnosis; an enhanced LPP to angry faces predicted better response to both CBT and SSRI and across diagnoses. Consistent with prior findings indicating that ERPs may be a more stable index of emotion processing than behavioral measures (Kappenman, MacNamara, & Proudfit, 2014; Kujawa et al., 2013), behavioral performance did not predict treatment response in this study.

[1] The results of independent samples *t*-tests also indicated no difference between males and females with regard to LPP or post-treatment anxiety severity (all *p*s > .18).

Our results are congruent with prior fMRI findings indicating an association between enhanced activation in higher-order visual regions to threat and better CBT response among adults with SAD (Doehrmann et al., 2013; Klumpp et al., 2013). This is noteworthy given that the LPP is conceptualized as reflecting activation in visual regions and prior findings linking the LPP to activation in visual regions as well as coupling between frontal and visual cortices (e.g., Keil et al., 2002; Moratti, Saugar, & Strange, 2011; Sabatinelli, Lang, Keil, & Bradley, 2007). As such, this congruence supports extending findings obtained using fMRI methods to the LPP as a potential neural predictor of treatment response among individuals with ADs.

Keeping in mind that the LPP indexes enhanced engagement with salient stimuli, our findings may reflect a number of mechanisms. From a deficit perspective, enhanced engagement at the neural level may index greater threat reactivity or emotion dysregulation (e.g., Dennis & Hajcak, 2009). Because threat reactivity and emotion dysregulation are treatment targets, youth with enhanced LPPs may comprise a subgroup with relatively greater threat reactivity and thus greater room for improvement. This interpretation would be consistent with Hum et al. (2013) who hypothesized that increased prefrontal activation during the N2 from pre- to post-treatment, which was associated with better CBT response, may have indexed increased cognitive control, which may have contributed to better treatment response. From a strength perspective, enhanced engagement at the neural level may reflect less avoidance and/or enhanced engagement with environmental stimuli, including with treatment. Youth with less avoidance and/or greater engagement may also be more likely to benefit from treatment (e.g., specific components such as exposures). These hypotheses are not only applicable to CBT wherein threat reactivity and emotion dysregulation are directly targeted but also to SSRI, which has been shown to be associated with reductions in threat reactivity (e.g., Mogg, Baldwin, Brodrick, & Bradley, 2004).

Of import, although pre-treatment symptom severity has been previously found to modestly predict treatment response (e.g., 20% of variance; Scholing & Emmelkamp, 1999), it was not a significant predictor in this sample. Conversely, our neural predictor of interest predicted post-treatment symptom severity, indicating that the LPP meaningfully outperformed a conventional clinical measure, consistent with previous fMRI findings (e.g., Doehrmann et al., 2013).

In contrast to our findings for the LPP to angry faces, we did not find a significant effect of the LPP to fearful faces predicting treatment response. Although this is *prima facie* surprising, a few pertinent hypotheses are noteworthy. First, prior findings indicate that angry facial expressions are more likely to *hold* the attention of anxious individuals whereas fearful expressions are more likely to *guide* their attention (Fox, Mathews, Calder, & Yiend, 2007). Given that the LPP indexes elaborative processing, it reflects held as opposed to guided attention, potentially explaining our results. Second, our stimuli involved faces looking directly at participating youth. From a functional evolutionary view of emotions, an angry face looking directly at someone and a fearful face looking at another location are clear with regard to the source of threat. Conversely, an angry face looking at another location or a fearful face looking directly at someone are ambiguous with regard to the source of threat (Adams & Kleck, 2002; Ewbank et al., 2009). Indeed, others have suggested that *direct angry* gaze and *averted fearful* gaze are what account for abnormally sustained attention of anxious individuals to threat (Fox, 2002; Fox, Russo, Bowles, & Dutton, 2001). For these reasons, it may be that the LPP to angry faces (which are more likely to hold attention) are a more sensitive predictor of treatment response than the LPP to fearful faces (which are more likely to guide attention). This specificity of LPP to angry but not fearful faces is both consistent and inconsistent with prior findings in

that some found effects for angry and others for fearful stimuli only. Differences in methods may, in part, account for the differences in findings (e.g., fMRI vs. ERPs; focus on either anger or fear but not the differential effects of these; different baseline [happy faces vs. neutral stimuli]), indicating the need for continued research in this area including to test the above hypotheses about the relative strength of the effects for angry faces.

A comment on the utility of ERPs as predictors of treatment response in clinical settings is worthy of note. Although measuring ERPs is certainly more complex and time-consuming than administering rating scale measures, in a review of the relevant literature Gabrieli et al. (2015) argue that noninvasive brain imaging is promising in identifying children and adults who are less or more likely to learn efficiently, develop criminal or unhealthy behaviors, and respond to treatment for a number of neurodevelopmental and neuropsychiatric disorders. However, this raises concerns related to the availability and cost of the neuroimaging equipment necessary to measure neural functioning. Not only is the relative cost efficiency and transportability of EEG encouraging in this regard, any economic analysis has to include the costs of current practices in the context of which patients are often inadvertently directed to treatments that are ineffective for them or in the context of which children have to exhibit academic impairment to receive educational treatments. For example, the cost of a neuropsychological assessment and report often exceeds that of an fMRI (Gabrieli et al., 2015). Thus, although measuring ERPs may be more complex and perhaps more time consuming than rating scale measures, the potential benefits of EEG measurements, both over rating scale measures with regard to consistency of prediction and over other neural measures with regard to cost effectiveness indicate that this method may be a promising one.

Limitations and Future Directions

Study limitations and future directions are as follows. First, although our sample was sufficiently large to detect a relationship between the LPP to angry faces and treatment response, we may have been underpowered to detect potentially smaller effects such as of the LPP to fearful or happy faces. Similarly, although the effect of LPP did not significantly vary by treatment type, our figure suggests a clear trend towards the relationship between LPP and post-treatment anxiety severity being stronger for SSRI than CBT. These considerations underscore the importance, as with as with any finding, of both replication and of extension to larger samples comparing different types of treatment.

Second, our sample included youth with separation, social, and/or generalized anxiety disorder; research is needed on diagnostic specificity of the associations we observed. Third, we included youth with ages spanning middle childhood through late adolescence. Although we accounted for age effects, our results are based on cross-sectional data, indicating a need for replication in longitudinal designs. Related, we did not assess and thus could not statistically account for pubertal status, which might influence emotional processing (e.g., Silk et al., 2009). Fourth, we relied on one measure of post-treatment functioning and the relationships of interest in this study should be examined using other indices of anxiety severity, other indices of clinical change such as academic and social functioning, and data collected from other informants, such as parent-, self- and teacher-report. Finally, the number of participants who had to be excluded due to noisy EEG data is a limitation and noise in data is a challenge with collecting neural measures in general, underscoring the importance of continued improvement in these technologies. Nevertheless, the portion of youth excluded due to noisy data in the current study is comparable to the portion of youth excluded for similar reasons in other ERP studies (e.g., Dennis & Hajcak, 2009; Janssen et al., 2016; Kujawa et al., 2015a).

Conclusions

The findings of this study indicate that individual differences in the LPP to angry faces prospectively predict CBT and SSRI response in anxious youth (in that an enhanced LPP predicted better treatment response). Thus, ERPs are a potentially useful neural predictor of treatment response, and with additional research with larger samples comparing different types of treatment, may ultimately become a helpful clinical decision-making tool.

Compliance with Ethical Standards

Ethical approval: All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent/assent was obtained from all participants.

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Table 1

Hierarchical Multiple Regression Analyses Predicting Anxiety Severity Following Treatment

	Angry LLPs - Post-Treatment PARS		Fearful LPPs - Post-Treatment PARS		Happy LPPs - Post-Treatment PARS	
Predictor	ΔF	β	ΔF	β	ΔF	β
Step 1	2.298					
Age		.027				
Depressive symptoms		.245				
Cognitive ability		-.378*				
Site		.086				
Step 2	.393					
Age		.048				
Depressive symptoms		.212				
Cognitive ability		-.337				
Site		.010				
Baseline anxiety severity		.183				
	ΔF	β	ΔF	β	ΔF	β
Step 3	4.810*		1.532		.484	
Age		-.053		-.028		.010
Depressive symptoms		.257		.234		.222
Cognitive ability		-.366		-.335		-.351
Site		.097		.084		.026
Baseline anxiety severity		.072		.123		.189
LPP		-.356*		-.220		-.122

Note. $*p \leq .05$

Angry LPP = late positive potentials following angry faces; Fearful LPP = late positive potentials following fearful faces; Happy LPP = late positive potentials following happy faces; PARS = Pediatric Anxiety Rating Scale; LPP = late positive potentials.