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Evidence for genetic contributions to neurobehavioral traits: Trait Fear/Fearlessness, Behavioral Inhibition, and the Late Positive Potential

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Abstract of the Dissertation

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Psychiatric disorders are the most common and costly forms of disease and injury worldwide. Despite this, our ability to accurately identify and treat these disorders is limited, due in part to deficient understanding of the underlying mechanisms of dysfunction. The current study aimed to identify genetically-influenced neurobehavioral traits—individual differences evident in both self-report and neural response—that might help improve classification and treatment of mental disorders. Results from event-related potential (ERP) components sensitive to emotional content demonstrated that a) neural processing of emotional content is heritable, b) the heritable traits of heightened trait fear and behavioral disinhibition are associated with unique emotional deficits measured by ERPs—high trait fear is associated with increased attention to threat, while behavioral disinhibition is associated with decreased attention to threat and reward, and c) the association between these heritable ERPs and self-reported traits is largely due to environmental influence. The results of this study should elucidate the pathways by which genes and environment interact to influence normal and abnormal behavior.

Dedication Page

For Sam and Miriam, with love.

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Introduction:

Psychiatric disorders represent complex targets for research. They manifest in diverse ways clinically and, in spite of ongoing attempts to identify discontinuous categories, are frequently comorbid with one another, suggesting fundamental common mechanisms (Clark, Watson, & Reynolds, 1995; Kessler et al., 2005; Krueger & Eaton, 2010; Krueger & Markon, 2006; Mineka, Watson, & Clark, 1998; Watson, 2005). Furthermore, despite recent assertions that many of these disorders of thought and behavior directly reflect abnormal neural activity or structure (France, Lysaker, & Robinson, 2007; Leshner, 1997), multiple steps likely separate any single neural signal from the expression of a complex (and often ill-defined) phenotype such as depression or schizophrenia operationalized based on behavioral observation and/or self-report (Miller, 2010; Miller, Engels, & Herrington, 2007; Poldrack, 2010).

Rather than linking brain activity to complex disorders, there is increasing effort to refine current diagnostic systems by linking direct measures of biological and physiological systems to intermediate constructs— specific deviations in behavior and thought, measured continuously, which may underlie multiple disorders (e.g., Carter & Barch, 2007; Cuthbert & Insel, 2010; Insel et al., 2010; Patrick, Durbin, & Moser, 2012; Sanislow et al., 2010). In line with this, the present proposal focuses on the identification of *neurobehavioral traits*—that is, continuous individual difference constructs with direct referents in both neurobiology and behavior (Depue & Iacono, 1989; Patrick & Bernat, 2010; Patrick, Durbin, et al., 2012). In particular, the present proposal seeks to use emotion-elicited Event Related Potentials (ERPs) in order to add to and refine research surrounding the neurobehavioral traits of behavioral inhibition and trait fear/fearlessness, two constructs which are thought to cut across multiple psychiatric disorders (Barlow, 2004; Kramer, Patrick, Krueger, & Gasperi, 2012; Patrick, Durbin, et al., 2012).

Identification of distinct patterns of neural response associated with each domain will be useful to ongoing efforts to establish neurobiologically-based approaches to the conceptualization of mental disorders. Additionally, establishing these connections will be helpful in refining both the physiological and self-reported phenotypes.

In addition, because psychiatric disorders are increasingly conceptualized as deriving at least in part from disruptions in affective responding (Allen, McHugh, & Barlow, 2008; Barlow, Allen, & Choate, 2004), identification of neural correlates of emotion processing which relate to these dispositional constructs will likely be critical. Trait fear and behavioral inhibition each have unique implications for processing of emotional material: for example, whereas trait fear is thought to reflect variation in "bottom-up" responding to threatening or provocative stimuli, behavioral inhibition is instead thought to capture individual differences in "top-down" abilities to control or regulate prepotent impulses (Patrick & Bernat, 2010; Patrick, Venables, et al., 2012). ERP components might therefore be particularly useful neurobiological links to these constructs, given that, though multiple components are sensitive to emotion, they do not all reflect identical cognitive-affective processes and may be functionally distinct (Hajcak, Weinberg, MacNamara, & Foti, 2012; Olofsson, Nordin, Sequeira, & Polich, 2008; Weinberg, Ferri, & Hajcak, 2013; Weinberg & Hajcak, 2011b). In this project, I will outline the presumed functional significance of multiple ERP components, and discuss the ways in which these distinct processes might relate to trait fear and behavioral inhibition. In particular, I will discuss the possibility that early components (i.e., the early posterior negativity, or EPN) represent relatively obligatory (i.e., bottom-up) processing of emotional content whereas later components (i.e., the complex of positive-going components known collectively as the Late Positive Potential, or LPP) might represent more flexible and elaborative engagement with emotional

content (reflecting both bottom-up and top-down influences; Hajcak et al., 2012; Olofsson et al., 2008; Weinberg et al., 2013; Weinberg & Hajcak, 2011b). Trait fearfulness might then relate specifically to enhancement of early, relatively obligatory, activity, whereas behavioral inhibition might be reflected across the time-course of processing, but particularly in later, sustained processing.

Finally, there is emerging evidence that variation in broad constructs like trait fear and behavioral inhibition is subject to substantial genetic influence (e.g., Hicks et al., 2006; Kendler, Prescott, Myers, & Neale, 2003; Kramer et al., 2012; Krueger et al., 2002). While there is evidence for heritability of non-affective ERP responses (e.g., Anokhin, Golosheykin, & Heath, 2008; Carlson & Iacono, 2006; Hall et al., 2006; Katsanis, Iacono, McGue, & Carlson, 2007; Polich & Bloom, 1999), there is to date little research examining genetic contribution to ERP components associated with affective processing (see, however, Anokhin, Golosheykin, & Heath, 2010). Using a large, genetically-informative sample of Monozygotic (MZ) and Dizygotic (DZ) twins, a primary aim of the present proposal is therefore to examine multiple event-related potential components across the time-course of emotion processing to determine which, if any, are heritable. Identification of genetically-transmitted variation in neural indices of affective responding may facilitate the identification of these neurobiological markers for neuropsychiatric disorders. Furthermore, evidence that the association between ERP components and self-reported dispositional factors is in part genetically-determined might help to elucidate the pathways by which genes influence normal and abnormal behavior.

In what follows, I will first discuss theories of how emotional information is processed by the brain, as well as how dispositional tendencies towards exaggerated or impaired processing (i.e., trait fear/fearlessness and behavioral inhibition) might be reflected across multiple

disorders. Additionally, I will outline existing research indicating that these neurobehavioral traits—conceptualized as latent constructs reflected in the domains of self-report and neurobiology—might be in part genetically-determined. Following this, I will discuss ERP components that might be useful in capturing variability in both bottom-up and top-down influences on emotion processing, as well as the extant research linking ERP components to trait fear/fearlessness and behavioral inhibition, all of which suggests that these components represent viable targets for neurobehavioral trait research.

Visual Attention, Emotion, and Bottom-up and Top-down Influences

At any given moment, the amount of information entering the human visual system far exceeds available processing resources (Anderson, Van Essen, & Olshausen, 2005; Driver, 2001; Parkhurst, Law, & Niebur, 2002; Rensink, O'Regan, & Clark, 1997; Treue, 2003). Only a small fraction of the information available in the visual field will be attended to, let alone encoded or remembered (Driver, 2001; Raichle, 2010; Rensink et al., 1997). In order to engage in the rapid and efficient selection process that determines which information is attended, and which information falls by the wayside, the brain must have mechanisms in place to ensure that salient visual information is not lost (Driver, 2001; Vuilleumier, 2005).

Two major attentional mechanisms are thought to govern this selection process. Bottom-up, or exogenous, mechanisms of attention—which are presumed to be rapid and relatively obligatory—appear to be driven by perceptual properties of visual stimuli (e.g., movement or color; Bacon & Egeth, 1994; Parkhurst et al., 2002; Theeuwes, 1994). Top-down, or endogenous, mechanisms are thought to reflect ongoing goals and intentions of the individual, and are relatively slower to capture or direct attention (Rock & Gutman, 1981; Tipper, Weaver, Jerreat, & Burak, 1994).

The clear boundaries drawn between bottom-up and top-down processes may be more conceptually helpful than anatomically plausible. As the field of cognitive neuroscience moves towards a more complex and non-hierarchical conceptualization of human neural activity that consists of ongoing, parallel, and iterative co-activation across multiple regions of the brain (Mesulam, 1998; Thielscher & Pessoa, 2007), evidence is emerging to suggest that top-down and bottom-up attentional processes act reciprocally and interactively (Mesulam, 1998; Mohanty, Egner, Monti, & Mesulam, 2009; Pessoa, 2008, 2010; Pessoa & Adolphs, 2010; Raichle, 2010).

However, emotional stimuli, or stimuli which relate to basic biological imperatives (e.g., to fight, flee, affiliate, feed, or mate), are a prime example of stimuli that appear to capture attention in a bottom-up fashion. Many have argued that—regardless of an individual's ongoing and idiosyncratic goals—emotional stimuli are *intrinsically* motivationally-salient, not because of their perceptual properties, but because of their content (Bradley, Codispoti, Cuthbert, & Lang, 2001b; Briggs & Martin, 2009; Lang & Bradley, 2010; Lang, Bradley, & Cuthbert, 1998; Lang, Greenwald, Bradley, & Hamm, 1993; LeDoux, 1996). In other words, attention is commanded by content that implies a motivational imperative (i.e., motivated attention; Lang, Bradley, & Cuthbert, 1997).

Consistent with this view, there is ample evidence that emotional stimuli are subject to prioritized processing. In the laboratory, viewing emotional pictures varying in content (e.g., the International Affective Picture System, or IAPS; Lang, Bradley, & Cuthbert, 2005) is typically used to study this selective attention. And evidence from such studies suggests that, compared to neutral stimuli, emotional cues are detected more easily (Fox et al., 2000; Öhman, Flykt, & Esteves, 2001; Tipples, Atkinson, & Young, 2002), more effectively capture and hold attention

(Armony & Dolan, 2002; Lang et al., 1997; Mogg, Bradley, De Bono, & Painter, 1997; Schupp et al., 2007; Vuilleumier, 2005), and are viewed for longer (Lang et al., 1997; Lang et al., 1993).

Perception of emotional stimuli is thought to be an ongoing and iterative process, characterized in the brain by feedback from subcortical sites (e.g., the amygdala), and/or occipitoparietal sites involved in attention, to frontal cortical sites (e.g., the Prefrontal Cortex, or PFC). This feedback loop is thought to facilitate a cascade of responses, including transient changes in experienced affect, dispositions to act, and changes in central and peripheral physiology in preparation for action (Hegdé and Felleman, 2007, Freese and Amaral, 2005, Lamme and Roelfsema, 2000, Lang and Bradley, 2010, Sugase et al., 1999, Vuilleumier, 2005). And indeed, a wide array of physiological systems are sensitive to emotional stimuli: compared to neutral stimuli, both pleasant and unpleasant pictures elicit larger electrodermal responses (Bradley, 2009; Codispoti, Bradley, & Lang, 2001), enhanced spinal reflexes (Bonnet, Bradley, Lang, & Requin, 1995; Both, Everaerd, & Laan, 2003; Dolan, 2002), and increased excitability in the motor cortex (Hajcak, Molnar, et al., 2007).

However, though it may be prioritized, processing of emotional stimuli is not *always* obligatory or automatic (Bishop, Duncan, & Lawrence, 2004; Bishop, Jenkins, & Lawrence, 2007; Liberzon et al., 2000; Pessoa, McKenna, Gutierrez, & Ungerleider, 2002; Pessoa, Padmala, & Morland, 2005). For instance, emotional stimuli may be made more or less salient through manipulations of attention, task demands, or even instructions to reappraise the content of the stimuli (Beauregard, Levesque, & Bourgouin, 2001; Dunning & Hajcak, 2009; Hajcak & Nieuwenhuis, 2006; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; MacNamara, Ferri, & Hajcak, 2011; Ochsner & Gross, 2005, 2007). This is thought to occur as a function of increased

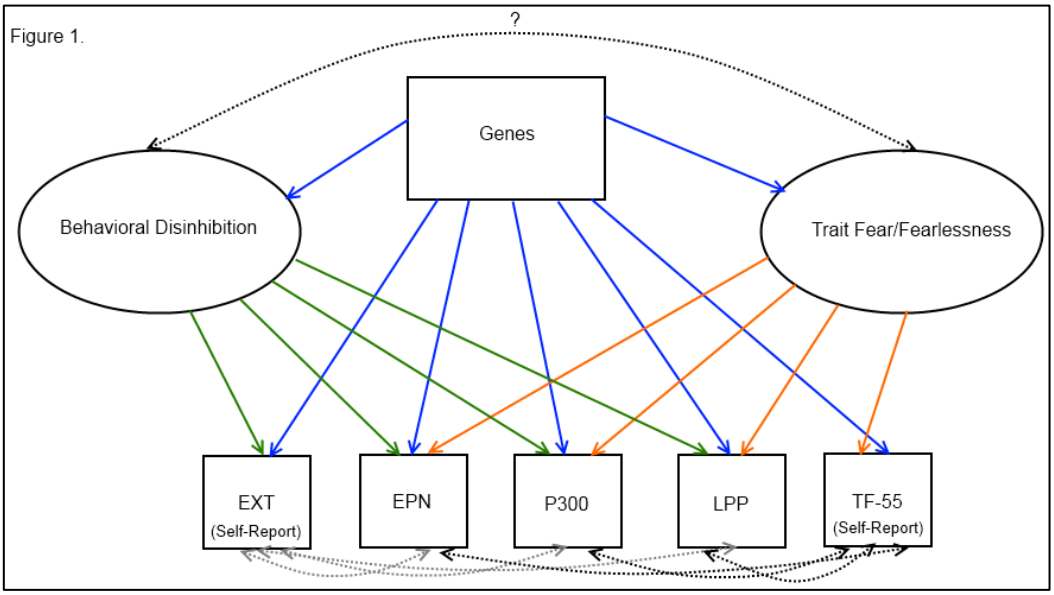
activity in the PFC, dampening activity of the limbic region (Hariri et al., 2003; MacNamara, Ferri, et al., 2011; Ochsner & Gross, 2007)

Furthermore, while enhanced attention to emotional compared to neutral content is normative, there is individual variability in the degree to which that attention is enhanced (Foti, Olvet, Klein, & Hajcak, 2010; Hajcak et al., 2012; Horan, Wynn, Kring, Simons, & Green, 2010; Kee, Green, Mintz, & Brekke, 2003; MacNamara & Hajcak, 2010; Weinberg & Hajcak, 2011a), and this variability might result from abnormal activity in limbic regions (Phan, Fitzgerald, Nathan, & Tancer, 2006; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002), prefrontal areas (Bechara et al., 2001; Hermann et al., 2007; Yang et al., 2005), or both (Blair, 2008; Davidson, 2002; Monk et al., 2008). Previous research has often focused on linking this variability to broad diagnostic categories. However, trait-like tendencies to over- or under-engage bottom-up or top-down mechanisms, or both, might also be reflected in the constructs of Trait fear/fearlessness and behavioral inhibition —traits that cut across multiple diagnoses. Through the neurobehavioral trait framework, discussed below, the present proposal attempts to better understand how this over- or under-engagement might be reflected in the domain of both self-report and neural response.

Neurobehavioral Traits

The concept of neurobehavioral traits represents an attempt to capture latent individual difference constructs via multiple modes of measurement across multiple domains (i.e., through the associations between neural activity and dimensional trait constructs derived from self-report or behavioral observation; Patrick & Bernat, 2010; Patrick, Durbin, et al., 2012; Patrick, Venables, et al., 2012). As indicated in Figure 1, self-report and neural activity are each thought to reflect distinct sources of variance, measured in different domains, contributing to a latent trait

construct (e.g., Trait fear, which is thought to have both subjective experiential and physiological expressions). Unlike research attempting to reconstrue psychological events as purely biological phenomena (France et al., 2007; Hyman, 1998), the neurobehavioral trait approach does not aim to recast the psychological constructs of trait fear and behavioral inhibition in purely neurobiological terms. Instead, this approach examines the extent to which latent constructs can be refined by the addition of reliable neural measures which may capture additional variability that is not reflected in the domain of self-report (e.g., Patrick, Venables, et al., 2012).



Some barriers exist to the field's ability to integrate neurobiological information into trait models. A trait is typically defined as a *habitual* pattern of activity which is relatively stable across time and situations, influences behavior, and differs across individuals (e.g., Eysenck, 1953). In order for a neural signal to be considered trait-like, there should be evidence for its reliability as well as its relationship with other variables to imply convergent validity (Patrick & Bernat, 2010; Vaidyanathan, Nelson, & Patrick, 2012; Weinberg, Riesel, & Hajcak, 2012). To date, however, the psychometric properties of many neural responses are unknown (see, for example, Patrick, Durbin, et al., 2012; Vul, Harris, Winkielman, & Pashler, 2009), making it

difficult to assess the degree to which these signals tap into trait constructs. One aim of the present proposal, therefore, is to assess the reliability of electrocortical indices of emotion processing in a large (N=479) sample.

Furthermore, there is enormous interest in the genetics of psychiatric disorders (e.g., Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Kendler & Prescott, 1999; McGuffin, Farmer, Gottesman, Murray, & Reveley, 1984). Yet the complexity of these psychological constructs makes it difficult to directly link the phenotypes to specific genes (Anokhin et al., 2010; Cannon & Keller, 2006; Gottesman & Gould, 2003). Psychiatric disorders are likely to a) reflect dysfunction across multiple systems and b) represent the sum of all environmental influences in addition to the activity of susceptibility genes (Cannon & Keller, 2006; Gottesman & Gould, 2003). Neurobiological marker models of psychiatric disorders assume a common genetic diathesis (Begleiter & Porjesz, 1999; Iacono, 1998) such that, in those instances in which specific traits or disorders have been linked to systematic variation in neural activity, the neural response should be transmitted alongside the behavioral phenotype. Identification of this intermediate neural phenotype—which relates in sensible ways to a disorder or area of dysfunction, but is less complex than the illness phenotype, and presumably relates more directly to the underlying neuropathology—is likely to be more useful in research concerned with genetic determination of dysfunction.

There is substantial evidence for genetic contributions to personality traits and disorders (Jang, Livesley, & Vemon, 1996; Livesley, Jang, & Vernon, 1998; Viken, Rose, Kaprio, & Koskenvuo, 1994), emotional response style (Gabbay, 1992), and self-reported intensity of emotional experience (Canli, Ferri, & Duman, 2009; Coccaro, Ong, Seroczynski, & Bergeman, 2011). This raises the possibility that *neurobehavioral* traits might also be genetically

determined. Yet, though there is evidence for genetic contributions to non-affective ERP responses (e.g., Anokhin et al., 2008; Carlson & Iacono, 2006; Hall et al., 2006; Katsanis et al., 2007; Polich & Bloom, 1999), there is little research examining the heritability of ERP components associated with affective processing (see, however, Anokhin et al., 2010). If individual differences in neural correlates of emotion processing are genetically determined, then these ERP components should be useful in investigations of the neurocognitive mechanisms mediating genetic influences on behavior. Consistent with this, the present proposal aims to identify neurobehavorial traits that are subject to genetic contributions. This may be helpful in establishing more specific etiological pathways for distinct forms of dysregulated affect. A genetically-determined neurobehavioral trait suggests a more specific liability marker which might represent a useful candidate for molecular genetic research. To that end, the proposed study is based on a large, genetically-informative sample (i.e., MZ and DZ twins) to apply multivariate genetic analyses to multiple ERP components and self-report measures. Additionally, I will examine the genetic and environmental sources of covariation between self-reported Trait fear/Fearlessness, Behavioral inhibition, and the emotion-modulated ERPs associated with them.

Trait Fear/Fearlessness

Fear is typically conceptualized as a relatively automatic and short-lived emotional response to a threatening stimulus, reflecting the engagement of an organism's defensive motivational system (Lang & Bradley, 2010; Lang et al., 1997, 1998; LeDoux, 1996). This defensive system—which involves the activation of sensory systems as well as central, autonomic and motor responses in preparation for action—is thought to be a circuit critically involved in survival, and one which typically prompts the organism to either flee or fight (Frijda,

1986; Lang & Bradley, 2010). Animal and human research concerned with the neural structures contributing to this fear response has largely focused on the activity and sensitivity of the bilateral amygdalae (Blanchard & Blanchard, 1972; Davis, 2006; Lang & Bradley, 2010; LeDoux, 1996; Phelps, 2006)—two small, almond-shaped collections of nuclei in the temporal lobes, which receive input from multiple regions of the brain. Following input from the cortex as well as sensory information from the thalamus and contextual information from the hippocampus (e.g., salient memories), the amygdala prompts a host of responses, including increased vigilance and information processing, as well as peripheral activation (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Lang & Bradley, 2010; Phelps, 2006) in the service of defensive actions. Phasic fear responses are therefore associated not only with increased BOLD activation in the amygdala (LaBar et al., 1998; Phan, Wager, Taylor, & Liberzon, 2002; Pine et al., 2001; Whalen et al., 1998) but also with increased activation in the visual cortex (Bradley et al., 2003), as well as increases in skin conductance response (e.g., Grillon & Ameli, 2001) and fear-potentiated startle (Vrana & Lang, 1990; Vrana, Spence, & Lang, 1988). Some have proposed that—to some extent—these fear responses can even bypass higher cortical structures, occurring relatively automatically (e.g., LeDoux, 1996).

Fear is adaptive, enabling the organism to evade or survive threat. But variability in the propensity to activate the defensive system has also been observed, suggesting that individuals fall along a continuous fear/fearlessness spectrum (Kagan & Snidman, 1999; Kagan, Snidman, Arcus, & Reznick, 1994; Kramer et al., 2012; Vaidyanathan, Patrick, & Bernat, 2008). Indeed, in a factor-analytic study of self-report measures of dispositional fear and harm-avoidance as well as psychopathy/fearlessness, Kramer and colleagues (2012) recently demonstrated that distinct self-report measures of trait fear and fearlessness capture a common, bipolar dimension.

The high end of the continuum is characterized by intense responsiveness to threat, interpersonal discomfort, and heightened harm/risk avoidance. The low end is instead characterized by interpersonal boldness, thrill-seeking, and a relative immunity to stress (Kramer et al., 2012; Vaidyanathan et al., 2008). Evidence from a large twin sample also indicates that this bipolar factor reflects strong genetic contributions (Kramer et al., 2012). Consistent with this, there is independent evidence for a genetic basis for variability in fear conditioning (Hettema, Annas, Neale, Kendler, & Fredrikson, 2003; Merrill, Steinmetz, Viken, & Rose, 1999; Royce, 1972), as well as associations between specific gene alleles and the degree of amygdala response to fear-provoking stimuli (e.g., Hariri et al., 2005; Hariri et al., 2002; Heinz et al., 2004). Finally, the fear-related anxiety disorders appear to arise from a similar genetic liability (Kendler et al., 1995). Evidence for a strong genetic contribution suggests a coherent etiology of this dimension, and further indicates that this trait factor might be a useful target for the investigation of neurobiological traits.

High levels of trait fear have been associated with multiple anxiety disorders, including agoraphobia, panic disorder, specific phobias and social phobias (Barlow, 2004; Hayden et al., 2007; Kochanska, Gross, Lin, & Nichols, 2003; Kramer et al., 2012; Krueger, 1999; Sylvers, Lilienfeld, & LaPrairie, 2011; Watson, 2005). Indeed, a lower threshold for the detection of threat, as well as chronic and protracted activation of the defensive system, is thought to represent a vulnerability marker for these forms of internalizing disorders (Patrick & Bernat, 2010; Rosen & Schulkin, 1998). Consistent with the notion that high levels of trait fear represent greater tonic activation of the defensive motivation system, individuals diagnosed with these disorders and non-clinical individuals high on measures of trait fear evince greater activation of the amygdala (Dilger et al., 2003; Stein et al., 2002), greater fear-potentiated startle (Cook,

Hawk, Davis, & Stevenson, 1991; Cook, Davis, Hawk, Spence, & Gautier, 1992; Corr, Kumari, Wilson, Checkley, & Gray, 1997; Corr et al., 1995; Vaidyanathan et al., 2008), and larger skin-conductance responses (Roth, Ehlers, Taylor, Margraf, & Agras, 1990; Weerts & Lang, 1978), suggesting a strong physiological component associated with the high end of this construct.

Low trait fear, on the other hand, is linked to multiple forms of externalizing problems, particularly psychopathy (Benning, Patrick, & Iacono, 2005; Blonigen, Hicks, Krueger, Patrick, & Iacono, 2005; Frick & White, 2008; Hare, 1965; Lykken, 1996; Patrick, 1994). Individuals diagnosed with these disorders frequently exhibit decreased amygdala response (Blair, 2008; Blair, Morris, Frith, Perrett, & Dolan, 1999; Mitchell, Richell, Leonard, & Blair, 2006; Patrick, 1994), an absence of normal patterns of startle potentiation (Benning et al., 2005; Patrick, 1994; Patrick, Bradley, & Lang, 1993; Vaidyanathan, Hall, Patrick, & Bernat, 2011; Vaidyanathan et al., 2008), and a blunted electrodermal response (Hare, Frazelle, & Cox, 1978; Lorber, 2004). In fact, hypoactive defensive reactivity has been proposed as a core deficit of psychopathy (e.g. Hare, 1965; Lykken, 1996; Patrick, 1994). Indeed, some have suggested that deficits in this system are responsible for the decreased empathy and impaired social learning that represent an important facet of the disorder (Blair, 2006).

Variability along the trait fear/fearlessness dimension has also been linked more specifically to individual differences in the processing of visually-presented *emotional* content. For instance, while threatening or fear-provoking images tend to enhance the defensive startle response across participants (Bradley, Codispoti, Cuthbert, & Lang, 2001a; Bradley, Cuthbert, & Lang, 1999), phobic individuals viewing images of the object of their fear show a further enhanced startle response compared to non-phobic individuals (De Jong, Visser, & Merckelbach, 1996; Hamm, Cuthbert, Globisch, & Vaitl, 1997; Vrana, Constantine, & Westman, 1992). In

contrast, psychopathic individuals (Levenston, Patrick, Bradley, & Lang, 2000; Patrick et al., 1993) and individuals low on measures of fear (Benning et al., 2005; Lissek & Powers, 2003; Vaidyanathan et al., 2008) tend *not* to demonstrate fear-potentiated startle by even highly-arousing negative content. Similarly, highly fearful individuals tend to show an enhanced amygdala response to idiographic fear images (Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005), while, compared to controls, individuals high on measures of psychopathy tend to show a blunted amygdala response to fearful faces and images (Blair, 2006; Kiehl et al., 2001; Marsh et al., 2008).

Combined, evidence suggests that the trait dimension of fear/fearlessness reflects individual variability in the propensity to activate the defensive motivation system. Furthermore, it appears as though this propensity is reflected not just in the behavioral phenotype but also in physiological and neural responses. Thus, the fear/fearlessness dimension appears to be a viable construct for investigations of neurobehavioral traits. Furthermore, the existing data suggest some specificity of emotional response at the high end of the trait continuum, such that these individuals are not broadly reactive to unpleasant stimuli (e.g., disgust-related material), but perhaps more selectively reactive to normative threat cues—or even idiographic threat cues (De Jong et al., 1996; Hamm et al., 1997; Sabatinelli et al., 2005; Vrana et al., 1992). On the other hand, the low end of the spectrum appears to be characterized by insensitivity to multiple emotional categories (e.g., Lissek & Powers, 2003; Vaidyanathan et al., 2008).

Behavioral inhibition

While trait fear is thought to reflect individual differences in the relatively automatic activation of the defensive motivational system, the construct of behavioral inhibition is thought to capture variability in the ability to exert "top-down" influence on behavior and affective

response (Patrick & Bernat, 2010; Patrick, Durbin, et al., 2012). Consistent with this, whereas the dimension of trait fear/fearlessness is thought to reflect the activity of an evolutionarily-adaptive system governing responses to threat driven by the limbic system, theories of behavioral inhibition/disinhibition instead point to the capacity of higher cortical structures to downregulate prepotent responses. Lesions in areas of the Prefrontal Cortex (PFC) result in impulsive, dysregulated behaviors (Berlin, Rolls, & Kischka, 2004; Cardinal, Pennicott, Lakmali, Robbins, & Everitt, 2001; Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994; Manes et al., 2002). Similarly, functional impairment in frontal regions has been associated with criminal behaviors (Sapolsky, 2004), alcohol and substance abuse (Bechara et al., 2001), and psychopathy (Blair, 2008, 2010). Disorders characterized by low levels of behavioral inhibition have also been linked to deficits in emotion processing. Emotional deficits in psychopathy are discussed above—these may be driven primarily by trait fearlessness, or by decreased behavioral inhibition, or both. But there is also evidence for emotion-driven impulsivity among substance-dependent individuals (Verdejo-García, Bechara, Recknor, & Pérez-García, 2007). Furthermore, though substance-addicted individuals show an enhanced response to *idiographic* drug images (Franken, 2003; Namkoong, Lee, Lee, Lee, & An, 2004; van de Laar, Licht, Franken, & Hendriks, 2004), they appear to show a *decreased* response to normative threat or appetitive images (Dunning et al., 2011).

Though research concerned with the neuroscience of behavioral inhibition has more typically focused on deficits, there is also evidence to suggest that increased metabolic activity in frontal regions is associated with *excessive* behavioral regulation, as observed in anxiety disorders like Obsessive-Compulsive Disorder and Generalized Anxiety Disorder (e.g., Baxter et al., 1987; Saxena, Brody, Schwartz, & Baxter, 1998). However, this is complicated by the fact

that, in emotional contexts, these disorders are often also characterized by a failure of prefrontal areas to downregulate activity of the amygdala (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010).

In the developmental literature, a bipolar dimension of impulsivity/behavioral disinhibition has also been identified and linked to theories of temperament (Barkley, 1997; Buss & Plomin, 1975; Hayward, Killen, Kraemer, & Taylor, 1998). Excessive behavioral inhibition in childhood is thought to confer risk for development of social phobia (Hayward et al., 1998), as well as specific phobias and panic (Mick & Telch, 1998; Rosenbaum et al., 1988; Rosenbaum, Biederman, Hirshfeld, & Bolduc, 1991), whereas childhood impulsivity is associated with a host of later disruptive behaviors and disorders (White et al., 1994). Additionally, these tendencies appear subject to substantial genetic contributions (Kendler et al., 2003; Krueger et al., 2002; Young, Stallings, Corley, Krauter, & Hewitt, 2000).

Recently, Krueger and colleagues (2007) have attempted to capture the construct of trait behavioral inhibition in the self-report domain via the *Externalizing Spectrum Inventory (ESI)*, a 100-item questionnaire with 23 subscales, all of which load substantially on an overarching factor capturing trait inhibition/disinhibition. Evidence from studies utilizing this questionnaire suggest that a common dispositional factor related to behavioral disinhibition contributes to a broad array of externalizing disorders and traits, such that high scores on this scale are associated with an increased probability of one of these disorders (Patrick, Venables, et al., 2012; Venables & Patrick, 2012). Furthermore, scores on this broad externalizing factor appear more heritable than the diagnostic categories they predict (Krueger et al., 2007). It is less clear how low scores on this scale might relate to internalizing disorders. Nonetheless, a heritable behavioral

disinhibition factor which represents a vulnerability marker for multiple disorders represents a likely target for neurobiological research.

In short, this project proposes that a great deal of individual variability in attention to emotion is determined via both bottom-up (related to trait fear) and top-down influences on emotion processing (related to behavioral inhibition; e.g., Patrick & Bernat, 2010; Patrick, Durbin, et al., 2012; Vaidyanathan et al., 2011). Of course, top-down and bottom-up directives can work interactively to influence the allocation of attention. The specific disorders associated with these broad trait domains might arise from problems in either or both domains, or from an interaction of the two (e.g., Blair, 2008; Patrick & Bernat, 2010). If these two neurobehavioral traits represent independent and/or additive contributions to emotional dysfunction, then consideration of them both can explain more variance in the observed phenotype.

Furthermore, the competitive and cooperative nature of attention in the context of emotion unfolds over time, such that different directives may exert more or less influence over the time-course of emotion processing (Gross & Thompson, 2007; Hajcak, Dunning, Foti, & Weinberg, in press; Ochsner, Bunge, Gross, & Gabrieli, 2002; Weinberg et al., 2013). The study of these processes requires techniques with excellent temporal resolution, which are capable of indexing dynamic processes (Hajcak et al., 2012). ERPs, which reflect the near-instantaneous activity of underlying neuronal populations, are therefore an ideal tool for this type of research. Thus, in what follows, I will discuss the ways in which multiple ERPs may be modulated by emotional content. In particular, I will focus on the Early Posterior Negativity (EPN), a component which likely reflects the *relatively* obligatory allocation of attention to emotional content. Following this, I will discuss the complex of positive-going deflections in the ERP waveform known

collectively as the LPP, which appears to reflect the confluence of bottom-up and top-down influences on sustained attention.

ERPs and Emotion

Multiple ERP components are sensitive to emotional stimuli (see, e.g., Hajcak, MacNamara, & Olvet, 2010; or Olofsson et al., 2008 for reviews). Indeed, the effects of both pleasant and unpleasant stimuli (compared to neutral) can be observed in ERP components occurring as early as 80 ms following stimulus onset (Mueller et al., 2009; Mühlberger et al., 2009; Olofsson & Polich, 2007) , and can continue for several seconds, evident even after stimulus offset (Hajcak & Olvet, 2008). Despite this persistent influence of emotional content, there is increasing evidence that early compared to late components might index different cognitive-affective processes (Hajcak et al., 2012; Olofsson et al., 2008; Weinberg & Hajcak, 2010, 2011b; Wiens, Sand, & Olofsson, 2011). Comparatively early ERP components (i.e., components occurring prior to 300 ms following stimulus onset) reflect the *relatively* obligatory capture of attention by emotional stimuli (Foti, Hajcak, & Dien, 2009; Hajcak et al., 2012; Olofsson et al., 2008; Weinberg & Hajcak, 2011b). Relatively later components (i.e., components occurring past 300 ms) are instead thought to reflect more flexible and elaborated processing of emotional stimuli (Olofsson et al., 2008; Weinberg & Hajcak, 2010, 2011b; Wiens, Sand, & Olofsson, 2011).

Relatively early ERPs sensitive to emotion

Early visual ERP components are thought to be driven principally by bottom-up properties of the stimuli themselves (Olofsson et al., 2008; Wiens, Sand, & Olofsson, 2011), meaning amplitude fluctuates *primarily* as a function of perceptual stimulus features such as spatial frequency (Carretié, Hinojosa, López-Martín, & Tapia, 2007), color (Cano, Class, &

Polich, 2009), complexity (Bradley, Hamby, Löw, & Lang, 2007), or size (Bradley et al., 2007; Cano et al., 2009; Carretié et al., 2007; Carretié, Hinojosa, Martín Loeches, Mercado, & Tapia, 2004). However, there is also increasing evidence that ERPs in this time-range may be sensitive to emotional content as well as physical properties of the stimuli themselves, or to the interaction of the two (Bradley et al., 2007). The early component of interest in the present proposal is the Early Posterior Negativity (EPN), a temporo-occipital negativity maximal at around 230 ms, which has been linked to increased visual processing of emotional compared to neutral stimuli (Foti et al., 2009; Schupp, Flaisch, Stockburger, & Junghöfer, 2006; Schupp, Junghöfer, Weike, & Hamm, 2003b). Though the EPN is sensitive to both pleasant and unpleasant emotional content (De Cesarei & Codispoti, 2006; Junghöfer, Bradley, Elbert, & Lang, 2001; Schupp, Flaisch, et al., 2006; Weinberg & Hajcak, 2010) there is some evidence to suggest that it is even larger following *pleasant* images compared to both neutral and unpleasant stimuli (Schupp, Flaisch, et al., 2006; Schupp, Junghöfer, Weike, & Hamm, 2004; Weinberg & Hajcak, 2010). Emotional modulation of the EPN is generally consistent across stimulus presentation durations, stimulus types, and both passive viewing and active tasks (Herbert, Junghöfer, & Kissler, 2008; Junghöfer et al., 2001), suggesting task parameters have relatively little influence on the processing of emotional content reflected in this component. Moreover, emotional modulation can be observed even when the task requires attention to be focused on non-emotional aspects of the stimuli (Kissler, Herbert, Winkler, & Junghofer, 2009; Schupp, Junghöfer, Weike, & Hamm, 2003a). For example, when participants are asked to count the number of checkerboard images intermixed with task-irrelevant emotional pictures, emotional modulation of the EPN is still observed (Schupp, et al., 2003a). In addition, some studies have shown that the EPN remains responsive to the emotional content of stimuli while performing a secondary auditory task

involving either low or high attentional demands (Schupp et al., 2008), or a target-identification task in which centrally-presented images are task irrelevant (Sand & Wiens, 2011) indicating the persistence of the influence of emotion on the EPN despite concurrent demands on attention (however, see also Wiens, Sand, Norberg, & Andersson, 2011). Collectively, these results suggest modulation of the EPN by emotional content reflects a *relatively* automatic process.

The Late Positive Potential (LPP) complex

The LPP, a centro-parietally-maximal component which follows closely on the EPN, appears uniquely suited to reflect the confluence of bottom-up and top-down influences on sustained attention. The LPP is a positive-going slow wave which becomes evident as early as 200 ms following stimulus onset, and which continues for the duration of picture presentation (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Foti & Hajcak, 2008; Hajcak & Nieuwenhuis, 2006; Junghöfer et al., 2001; Lang et al., 1997). Recent research suggests that the LPP may consist of a series of overlapping positive deflections in the waveform (Foti et al., 2009; MacNamara, Foti, & Hajcak, 2009; Weinberg & Hajcak, 2011b) the first of which is morphologically and temporally similar to the P300, a component which is among the most extensively researched in the ERP literature.

The P300 appears sensitive to the motivational salience of stimuli, and is typically observed in non-affective paradigms in which an infrequent target stimulus is presented in a context of frequent non-target, or standard, stimuli (Polich, 2007, 2010). Yet the P300 is larger for targets even when targets and standards are equally probable, suggesting that task relevance or the instructed salience of the stimulus itself is sufficient to potentiate the P300 (Duncan Johnson & Donchin, 1977).

Emotional stimuli may be intrinsically motivationally-relevant, independent of task parameters, and may be thought of as "natural targets." Consistent with this, modulation of a P300-like component is also frequently observed for emotional (both pleasant and unpleasant) compared to neutral stimuli (Ferrari, Codispoti, Cardinale, & Bradley, 2008; Foti et al., 2009; Johnston, Miller, & Burleson, 1986; Weinberg & Hajcak, 2011b) suggesting that processes indexed by the P300 may be linked broadly to motivation, determined either through top-down or bottom-up imperatives, or both (Ferrari, Bradley, Codispoti, & Lang, 2010; Weinberg, Hilgard, Bartholow, & Hajcak, 2012). Though it is difficult to determine definitively whether two components derived under different experimental conditions are the same, similarities in terms of their topography, timing, and response to task parameters suggest that the P300 observed in non-affective target detection tasks may reflect similar processes as the early portion of the LPP observed in emotion research. In order to avoid the awkward and confusing use of "early late positive potential," I will use "P300" in the following paper to refer to the portion of the LPP occurring between 300 and 600 ms.

The heritability of the P300 elicited by non-affective targets has also been explored extensively (Iacono, Malone, & McGue, 2003; Katsanis, Iacono, McGue, & Carlson, 1997), and twin and family studies have identified substantial genetic contributions to the magnitude of the component (Eischen & Polich, 1994; Hall et al., 2006; Katsanis et al., 2007; Polich & Bloom, 1999). Additionally, extant research suggests this component may represent a genetically-linked vulnerability marker for a number of distinct disorders characterized by deficits in behavioral inhibition, including schizophrenia (Bramon et al., 2005; Weisbrod, Hill, Niethammer, & Sauer, 1999), alcohol dependence/abuse (Perlman, Johnson, & Iacono, 2009; Polich & Bloom, 1999), substance use disorders (Iacono et al., 2003; Markin, Perlman, & Iacono, 2008), and

externalizing spectrum disorders more broadly (Nelson, Patrick, & Bernat, 2010), suggesting it is a useful tool for investigations of neurobehavioral traits. To date there is only one study using emotional facial stimuli demonstrating heritability of the P300 (Anokhin et al., 2010); however, this study looked at genetic contributions to the overall P300, and did not examine potential genetic contributions to affective processing more specifically.

Following the P300 is a sustained slow-wave component/series of components, known as the LPP. Like the prototypical P300, the sustained LPP is larger following both pleasant and unpleasant compared to neutral stimuli (Cuthbert et al., 2000; Keil et al., 2002) and is sensitive to emotional images (Cuthbert et al., 2000; Foti et al., 2009; Pastor et al., 2008), words (Fischler & Bradley, 2006; Kissler et al., 2009; Tacikowski & Nowicka, 2010), and even emotional hand gestures (Flaisch, Häcker, Renner, & Schupp, 2011). Furthermore, there is some evidence that the magnitude of the LPP is correlated with skin conductance and self-reported affective arousal in response to individual pictures (Cuthbert et al., 2000). The sustained positivity elicited by emotional compared to neutral images can persist well beyond picture offset (Codispoti, Mazzetti, & Bradley, 2009; Hajcak & Olvet, 2008), and it appears to shift in distribution over the course of affective picture processing, progressing from an early parietal distribution to a more centrally-maximal distribution (Foti et al., 2009; MacNamara et al., 2009). While earlier components are highly sensitive to the perceptual properties of stimuli (Wiens, Sand, & Olofsson, 2011), the LPP is not, appearing to track content rather than complexity or size (De Cesarei & Codispoti, 2006; Wiens, Sand, & Olofsson, 2011).

Also unlike earlier ERP components, which appear to index the relatively gross discrimination of emotional from non-emotional processes, the LPP can reflect more fine-grained distinctions within emotional categories such that emotional modulation of the LPP is

enhanced for those stimuli most directly relevant to biological imperatives, irrespective of arousal ratings (e.g., threat, mutilation, and erotic images; Briggs & Martin, 2009; Schupp, Cuthbert, et al., 2004; Weinberg & Hajcak, 2010). For example, erotic images within the pleasant category elicit a larger electrocortical response than neutral images of objects, which are also rated as less arousing. But the LPP elicited by erotica is also larger than that elicited by "exciting" images (e.g., content related to sports, cars, or feats of daring), though both erotic and exciting images are rated as highly arousing and pleasant (Weinberg & Hajcak, 2010). This is presumably because exciting images have little direct bearing on survival or reproduction (Briggs & Martin, 2009), and as such, may not necessitate the same degree of sustained attention. These data further suggest a dissociation between self-reported arousal and the LPP; though the LPP tends to be enhanced by images which participants rate as more arousing, the LPP is not *only* reflecting arousal.

The LPP also appears to be *functionally* distinct from the EPN and P300. For example, in one study, participants were asked to identify a target—either a circle or a square—which was both preceded and followed by task-irrelevant pleasant, neutral, or unpleasant IAPS images. Consistent with previous research, (Mitchell et al., 2008; Mitchell et al., 2006) responses to imperative targets were slowed by the presence of the task-irrelevant emotional images (Weinberg & Hajcak, 2011b). Although multiple ERP components were enhanced by the task-irrelevant emotional stimuli (i.e., EPN, P300) only the later sustained LPP predicted the degree of behavioral slowing: The larger the LPP, the slower the response to targets. This was true between participants, such that individuals with an enhanced LPP to task-irrelevant images were also slower to respond to targets. But it was also true within participants, in that, for each individual, slower trials tended to be preceded by pictures that elicited a larger LPP.

Additionally, the LPP predicted variation in neural activity elicited by the targets: a larger LPP to task-irrelevant IAPS images was related to a reduction in the magnitude of the P300 elicited by targets. These results suggest that the continued elaboration and encoding indexed by the LPP uniquely relates to interference with sustained attention to targets, as reflected in the subsequently slower response times and reduced P300s to targets in this task.

There is also reason to believe that bottom-up and top-down influences jointly influence the processing of emotional stimuli in a way that is relatively independent of one another, and that this, too, is reflected in the sustained LPP. For example, a recent study in our lab utilized a variant of an "oddball" paradigm in which targets representing a given valence category (i.e., pleasant, neutral, or unpleasant) were presented infrequently within a stream of images from a different affective category (e.g., a single pleasant picture presented in a stream of unpleasant pictures; Weinberg, Hilgard, et al., 2012). Thus, in this study, targets were identified by virtue of their valence (i.e., pleasant, neutral, unpleasant). Targets (whether emotional or neutral) and emotional stimuli (whether targets or non-targets) were both associated with an enhanced P300 (Weinberg, Hilgard, et al., 2012). These effects appeared additive, rather than interactive, such that emotional targets elicited the largest response of all, and the impact of target status was similar for both emotional and neutral images (see also: Ferrari et al., 2010; Ferrari et al., 2008). In comparison, the later LPP appeared uniquely sensitive to target status (Weinberg et al., 2012), consistent with hypotheses that this later component reflects more flexible, sustained, and elaborative processes that might be more related to task-relevant imperatives in this context (Foti & Hajcak, 2008; MacNamara, Ferri, et al., 2011; MacNamara et al., 2009; MacNamara, Ochsner, & Hajcak, 2011; Olofsson et al., 2008; Weinberg & Hajcak, 2011b).

Anatomical sources of the EPN and LPP

Because ERPs are bioelectrical signals conducted through the brain, meninges, skull, and scalp, they are subject to spread as the signal seeks paths of low resistance; precise identification of primary neural contributors is therefore often difficult. Furthermore, neural activity recorded from an electrode exterior to the skull reflects the simultaneous and summed activation of many, many thousands—even millions—of neurons (Luck, 2005, 2012). In addition, there is evidence that scalp-recorded ERPs can reflect large-scale neuronal synchronization across spatially distributed neuronal networks (Pizzagalli, 2007). Nonetheless, a number of mathematical solutions have been developed which are helpful in inferring neural sources of ERPs (reviewed in Pizzagalli, 2007). In short, scalp-recorded ERPs likely reflect the activity of a coordinated *network* of neurons, which in some instances may represent the activity of a single anatomical node, but which may also reflect dynamic exchanges between brain regions, as well as widespread neuromodulatory activity (de Rover et al., 2012; Hajcak, MacNamara, et al., 2010). That is, it may be more fruitful to think about ERPs as indexing the activation of neural networks, rather than activity of a single and isolated region of the brain.

The occipital distribution of the EPN has led many to suggest the component is generated by the primary visual cortex (e.g., Schupp, Stockburger, et al., 2006). In terms of the P300 and LPP, however, there are a number of additional features of the complex that might make source localization difficult. For instance, the sustained LPP has a broad spatial distribution, and appears to reflect a series of neural responses overlapping closely in time and space (Foti et al., 2009; MacNamara et al., 2009; Weinberg & Hajcak, 2011b). Furthermore, the shift in the distribution of the LPP over time from a relatively focal posterior distribution to a broader and more anterior distribution (Foti et al., 2009; Hajcak, MacNamara, et al., 2010; MacNamara et al., 2009) suggests that processing of emotional images may engage multiple neural networks over the

course of picture viewing. This is consistent with fMRI research suggesting that affective visual information traverses multiple processing stages and sites, from early visual to prefrontal areas (Thielscher & Pessoa, 2007).

Nonetheless, recent work has attempted to identify neural generators of the P300/LPP complex. Three studies implicate areas of the visual cortex as likely generators. For example, using minimum norm source localization methods, Keil and colleagues (2002) estimated the neural sources to lie in the occipital and posterior parietal cortex. This is consistent with evidence from fMRI (Bradley et al., 2003; Lang et al., 1998) suggesting emotional pictures trigger increased activation in secondary visual processing sites in the lateral occipital cortex, extending up the dorsal stream to the parietal cortex. Variation in the LPP has also been related to neural activity in occipital, parietal, and inferotemporal regions of the brain in a study that combined EEG and fMRI measures from the same participants (Sabatinelli, Lang, Keil, & Bradley, 2007). Though direct contributions from the amygdala to the magnitude of the LPP have not been identified, some have suggested, based on detailed animal models, that the LPP might reflect re-entrant projections from the amygdala to multiple areas of the visual cortex (e.g., Lang & Bradley, 2010). This postulated feedback mechanism is also consistent with models of selective attention, which argue that this type of re-entrant signal might act to prioritize salient stimuli (Sabatinelli, Keil, Frank, & Lang, 2012).

Finally, observations that the P300/LPP complex reflects both bottom-up and top-down influences suggests the involvement of prefrontal cortical areas acting in conjunction with limbic areas to direct attention. Consistent with this, both electrical stimulation (Hajcak, Anderson, et al., 2010) and functional activation (MacNamara, Ferri, et al., 2011) of the dorsolateral prefrontal cortex (DLPFC) during emotional picture viewing appears to decrease the magnitude of the LPP,

suggesting a role for frontal areas. And a recent attempt to localize the magnetic homologue of the LPP (mLPP) indicates sources in the bilateral occipito-parietal and right prefrontal cortex, suggesting the LPP is generated by a fronto-parietal network (Moratti, Saugar, & Strange, 2011). All told, it appears that the magnitude of the LPP derives from ongoing communication amongst multiple brain regions that sustain visual attention. Though this highlights the spatial imprecision of the component (and the ERP technique more generally) it also points to the LPP's utility as an online index of concerted neural efforts to direct and maintain visual attention.

Relationship of EPN, P300, and LPP to individual difference variables:

While no studies to date have examined the association of any of the emotion-modulated ERP components discussed above with the broad constructs of trait fear and behavioral inhibition, there are multiple studies linking enhancements or decrements in ERP components to diagnoses associated with each of these dispositional domains. For instance, the EPN (Michalowski et al., 2009; Van Strien, Franken, & Huijding, 2009), and P300 and LPP (Leutgeb, Schäfer, & Schienle, 2009) are enhanced in spider-phobic individuals viewing spider pictures. All three components are also enhanced in socially-phobic individuals viewing angry and fearful faces (Moser, Huppert, Duval, & Simons, 2008; Mühlberger et al., 2009). Similarly, both the P300 and LPP are enhanced by body-related words in panic disorder patients (Pauli et al., 1997). In contrast, individuals high on measures of psychopathy tend to show a reduced LPP to unpleasant images compared to healthy controls (Samimi Sadeh & Verona, 2012), suggesting that these individuals may fail to engage in ongoing elaboration of unpleasant material. Furthermore, these results appear to be driven by emotional deficits in psychopathy, rather than deficits related to behavioral inhibition.

In non-affective research using the target-elicited P300, an extensive literature documents a relationship between a reduced P300 and a variety of disorders and tendencies suggestive of deficits in behavioral inhibition (e.g., Bernat, Nelson, Steele, Gehring, & Patrick, 2011; Brigham, Herning, & Moss, 1995; Iacono et al., 2003; Iacono, Malone, & McGue, 2008). High scores on the broad externalizing factor underlying these multiple disorders are also related to this reduced P300 (Patrick et al., 2006). Furthermore, the relationship between P3 and general externalizing proneness primarily reflects overlapping genetic influence (Hicks et al., 2006). There is no work to date exploring how *emotional* modulation of the P300 might be associated with behavioral inhibition. However, though larger LPPs are elicited by idiographic substance cues in alcohol- (Namkoong et al., 2004), heroin- (Franken et al., 2003) and cocaine-addicted individuals (Franken et al., 2004; van de Laar et al., 2004), there is also evidence that cocaine-addicted individuals exhibit a *reduced* LPP to normative emotional images (Dunning et al., 2011). Finally, anxiety appears to relate to an enhanced LPP in certain contexts (MacNamara & Hajcak, 2009, 2010); furthermore, there is evidence that the enhanced LPP in anxiety may be characterized by a failure of frontal areas to inhibit attention to emotion (MacNamara, Ferri, et al., 2011; MacNamara & Hajcak, in prep)

Combined, these data suggest that the EPN, P300, and LPP may represent biological markers of traits underlying multiple internalizing and externalizing disorders. However, as discussed above, any of these broad disease categories and their associated neural responses to emotional content could arise from abnormalities in trait fear or behavioral inhibition, or both, acting in an additive or interactive fashion. Use of continuous measures of these trait constructs across a large sample should allow for more specificity, as well as examination of whether these

relations between ERPs and the two self-reported trait constructs occur interactively or independently.

Specific Aims and Hypotheses:

1. As noted above, a first step in identifying neurobehavioral traits will be establishing the psychometric properties of measures in both the self-report and biological domains. The reliability of the self-report measures used in the project is well-established (Kramer et al., 2012; Krueger et al., 2007; Venables & Patrick, 2012). However, the psychometric properties of emotion-modulated ERPs have not yet been demonstrated. A basic aim of the present proposal, therefore, will be to calculate the split-half reliability of the components I propose to examine. I expect that both the P300 and the sustained LPP will demonstrate high levels of reliability. Because the EPN is more affected by perceptual properties of stimuli, it may be somewhat less reliable, insofar as images were not equated for complexity and color.

2. There is emerging research to suggest that the multiple ERP components sensitive to the affective content of stimuli do not reflect identical cognitive-affective processes and may be functionally distinct. The present study seeks to determine which of these processes and components might also be genetically-determined, in hopes of identifying neurobehavioral marker(s) of genetically-determined processing of emotional information. In keeping with previous non-affective work, I expect that the P300 will be heritable, and, further, that emotional modulation of the P300 by both pleasant and unpleasant images will be heritable, insofar as both categories of emotional images may be considered natural targets.

3. Additionally, this project seeks to clarify which, if any, components might best represent a neural index of affective processing associated with behavioral inhibition and defensive reactivity which is at least partially genetically-determined. Because the EPN, P300, and LPP vary in their sensitivity to specific picture categories, each component will be examined in response to the broad semantic categories of pleasant, neutral, and unpleasant. Consistent with previous work in fear disorders and psychopathy, I predict that high trait fear will be associated with an increased EPN, P300, and sustained LPP response to unpleasant pictures, while low trait fear will be associated with a relatively blunted response to this content. In contrast, I expect that low behavioral inhibition will be associated with a decreased response across the time-course of affective processing to both pleasant and unpleasant IAPS images. However, to the extent that the LPP reflects relatively greater top-down influence in sustaining and directing attention to emotion, a particularly strong association with behavioral inhibition might be observed with later portions of the LPP.

4. Finally, consistent with the belief that emotional modulation of ERP components may represent a biological marker for the two trait dimensions of interest, I predict substantial genetic contribution to the association between the emotion-modulated P300 and continuous measures of trait fear and behavioral inhibition.

Method

Participants

Participants consisted of 510 (258 female, 252 male) twins (260 MZ, 248 DZ) recruited from the University of Minnesota Twin Registry and screened for hearing and visual impairments prior to testing. Thirty-one participants were excluded from current analyses due to excessive artifact in

the EEG recordings (n = 16), discontinuation of participation (n = 6), or technical problems with the EEG collection (n = 9), resulting in 479 participants in the final analyses (244 MZ, 235 DZ; 242 males, 237 females). The mean age of study participants was 29.39 years (SD = 4.84; range = 22-38) and the racial composition was as follows: Caucasian, 96.5%; African American, .6%; Hispanic, .4%; Native American, .8%; mixed race, .8%; other/missing, 1.3%. Procedures for the study were approved by the University of Minnesota's institutional review board (IRB), and all participants provided informed written consent prior to testing. Data for the current report were collected as part of a larger protocol for which participants received $100 as compensation along with reimbursement for travel expenses.

Self Report

*Behavioral inhibition (BI)***:** Behavioral inhibition was assessed via the *Externalizing Spectrum Inventory* (ESI: Krueger, et al., 2007). The ESI is a 100-item scale consisting of 23 unidimensional construct scales, each assessing distinct facets of externalizing tendencies, including: excitement seeking, irresponsibility, impulsivity, aggression, rebelliousness, blame externalization, and alcohol, drug, and marijuana use/problems. Items from this scale were summed to form an index of behavioral inhibition, with high scores signaling *decreased* behavioral inhibition.

*Trait fearfulness (TF)***:** Participants were assessed for levels of dispositional fear via a recently-established omnibus measure (Kramer et al., 2012; Patrick & Bernat, 2010) consisting of 55 items drawn from other self-report inventories of fear and fearlessness, including: the Fear Survey Schedule-III (Arrindell & Van Der Ende, 1986), the Fearfulness subscale of the EAS Temperament Survey (Buss & Plomin, 1986), the Harm Avoidance subscale of the Temperament and Personality Questionnaire (Cloninger, 1987), subscales comprising Factor 1 of the

Psychopathic Personality Inventory (Lilienfeld & Andrews, 1996), and the Thrill/Adventure Seeking subscale of the Sensation Seeking Scale (Zuckerman, 1979). Items on this scale were summed for form an index of Trait fear/Fearlessness, with high scores indicating high levels of trait fear.

Experimental Stimuli and Design:

Participants viewed a series of 90 pictures consisting of 30 pleasant, 30 neutral and 30 unpleasant scenes selected from the International Affective Picture System (IAPS; Lang et al., 2008).[1] Pictures were presented for 6s followed by an intertrial interval of 12s. Pleasant pictures included exciting (e.g. skydiving, river rafting), erotic scenes (e.g. opposite-sex nude individuals and intimate couples), and affiliative (e.g., babies and small animal) scenes. Unpleasant pictures included scenes of mutilation (e.g. mutilated bodies, serious wounds) and threat (e.g. pointed guns, looming attackers, threatening animals). Neutral pictures consisted of scenes of neutral people, household objects, and kitchen utensils. Within the pleasant valence category, erotic pictures differed for men and women, in order to equate these categories for normative ratings of valence and arousal across genders.[2]

During 81 of the 90 picture stimuli, noise probes (50 ms, 105dB, 10μs rise time) were presented 3, 4, or 5 s after stimulus onset. For 6 of the remaining 9 pictures, probes were

[1] The 90 IAPS pictures were as follows: pleasant, 5621, 8030, 8080, 8185, 8186, 8370, 8200, 8490, 8180, 4659, 4660, 4687, 4695, 4670, 4681, 1710, 2040, 2150, 2340, 1440, 2154, 2080, 2071, 2058, 2350, 1750, 2530 [males only: 4210, 4180, 4232; females only: 4572, 4542, 4538]; neutral, 7004, 7010, 7020, 7041, 7175, 7185, 7000, 7187, 7035, 7179, 7491, 7705, 7100, 5740, 7050, 7150, 5510, 7059, 7510, 7700, 2038, 2190, 2480, 2840, 2393, 2890, 2102, 2280, 2397, 2215; and unpleasant: 3053,3102, 3080, 3120, 3130, 3000, 3060, 3010, 3071, 1525, 1050, 1205, 1300, 2811, 6230, 6250, 6260, 6300, 6370, 6830, 2692, 6200, 6210, 6213, 6243, 6244, 6570, 3064, 3280, 1220.

[2] Mean valence and arousal normative ratings (Lang et al., 2008) for each valence category by gender were as follows: For females, pleasant: valence (mean = 7.58, SD = .79); arousal (mean = 5.86, SD = 1.01); neutral: valence (mean = 4.96, SD = .34); arousal (mean = 2.71, SD = .51); and unpleasant: valence (mean = 2.13, SD = .72); arousal (mean = 6.77, SD = .68). For males, pleasant: valence (mean = 7.49, SD = .47); arousal (mean = 6.05, SD = 1.27); neutral: valence (mean = 4.94, SD = .30); arousal (mean = 2.71, SD = .62); and unpleasant: valence (mean = 2.93, SD = .87); arousal (mean = 6.17, SD = .62).

delivered 1, 1.5, or 2s following picture offset. Eight slide presentation orders were used for males, and 8 for females. Within and between orders, pictures and noise probes were counterbalanced such that valence categories (pleasant, neutral, and unpleasant) were represented equally across orders at each serial position, with the following constraints: no more than two slides valence occurred consecutively within any stimulus order; pictures of the same content category never appeared consecutively or across orders, pictures were rotated as to serve in both probed and unprobed trials.

Physiological Data Recording and Reduction Procedures:

During the experiment, participants viewed the picture stimuli on a 21" computer monitor situated approximately 1 m away, at eye level, while seated in a comfortable recliner. Data collection was performed using two PC computers, one equipped with E-Prime software (MEL software, Inc) for stimulus delivery and the other with Neuroscan Acquire software for physiological data acquisition. ERP activity was recorded from 53 scalp sites positioned according to the 10-20 system (AF3,AF4, AFZ, C1, C2, C3, C4, C5, C6, CP1, CP2, CP3, CP4, CPZ, CZ, F1, F2, F3, F4, F5, F6, F7, F8, FC1, FC2, FC3, FC4 ,FCZ ,FP1 ,FP2, FPZ, FT7, FT8, FZ, O1, O2, OZ, P1, P2, P3, P4, P5, P6, P7, P8, PO3, PO4, POZ, PZ, T7, T8, TP7, and TP8) using Neuroscan Quik-Caps with sintered Ag-AgCl electrodes. Electrodes were positioned above and below the left eye to monitor vertical electrooculographic (VEOG) activity and adjacent to the outer canthi of the left and right eyes to monitor horizontal electrooculographic (HEOG) activity. All electrode impedances were kept below 10 KOhms. EEG signal activity was recorded using electrode site Cz as the on-line reference and applying an analog band pass filter of .05-200 Hz prior to digitization at 1000Hz. The raw EEG data were re-referenced offline either to the average of the left and right mastoids (LPP) or to an overall electrode average (EPN;

see below) and low-pass filtered with a high cutoff of 30 Hz. Eye-blink and ocular-movement corrections were performed according to the procedures specified by Gratton, Coles and Donchin (1983).

Subsequent to these steps, a partially automated protocol was used to identify artifactual data for rejection. Data for individual channels were flagged for rejection if a voltage deflection of more than 50.0 μV occurred between sample points, if a deflection greater than 300.0 μV occurred within a segment, or if a voltage difference of less than .50 μV was evident within 100 consecutive ms. Data for the remaining, unflagged trials were inspected visually to detect any other artifacts warranting rejection.

EEG activity was examined across an interval extending from 200 ms prior to picture onset up to 3,000 ms afterward. ERP waveforms were constructed by separately averaging pleasant, neutral, and unpleasant picture trials. Each ERP average was baseline-corrected relative to activity in the 200 ms pre-stimulus window.

Affective modulation of the EPN is maximal at occipital sites, and a linked mastoid reference subtracts a substantial portion of this activity from the average (Hajcak et al., 2012). Furthermore, most studies examining the EPN utilize an average reference scheme (e.g., Schupp et al., 2003a; Schupp, Junghöfer, et al., 2004; Wieser et al., 2006), while most studies examining the LPP use a mastoid reference scheme (e.g., Cuthbert et al., 2000; Ito, Larsen, Smith, & Cacioppo, 1998; Schupp et al., 2000; Weinberg & Hajcak, 2010). In order to best capture the activity of the EPN, and to make our results more easily comparable to published work, each subject's data was re-referenced to the average of all electrodes for the purposes of scoring the EPN; all other data presented were referenced to the average of the mastoids. The EPN was then

scored as the average activity at Oz, between 175 and 275 ms (Foti et al., 2009; Hajcak et al., 2012; Schupp, Flaisch, et al., 2006; Weinberg & Hajcak, 2011b).

Because previous research (Foti et al., 2009; Weinberg & Hajcak, 2011b; Weinberg, Hilgard, et al., 2012) has demonstrated that important information about the time course of emotional responding may be reflected in differences between early and later portions of the LPP, the LPP was scored in four time-windows following stimulus onset: 300-600 ms, 600-1,000 ms, 1,000-2,000 ms, and 2,000-3,000 ms. In addition, there is evidence that the LPP shifts in distribution from a relatively focal centro-parietal distribution early after stimulus presentation to a more diffuse and frontal distribution later in time (Hajcak, MacNamara, et al., 2010; Hajcak & Olvet, 2008; Olofsson et al., 2008). Each time-window of the LPP was therefore scored at both Pz and Fz to capture this shifting distribution over time (Cuthbert et al., 2000; Foti & Hajcak, 2008; Foti et al., 2009; Keil et al., 2002).

Finally, in order to assess the split-half reliability of each of these components, new averages were created. For each subject and each picture type, two separate averages were created for each of the components noted above; one for even-numbered trials and one for odd-numbered trials (e.g., the EPN elicited by pleasant pictures on even trials, and the EPN elicited by pleasant pictures on odd trials).

Statistical Analyses:

The following statistics were conducted using SPSS (Version 17.0):

Split-half reliability: Pearson's *r* and Intraclass Correlations (ICC) were used to assess the relationship between odd and even trials for the pleasant, neutral, and unpleasant categories.

Affective modulation: First, in order to establish emotional modulation was occurring amongst the broad semantic categories, ten 3-way (valence category) repeated-measures

ANOVAs were conducted to examine the effects of valence category on each of the components scored at each site (i.e., the EPN, and the three time-windows of the LPP, at Pz and Fz). Greenhouse-Geisser correction was applied to *p* values associated with multiple-df, repeated-measures comparisons when necessitated by violation of the assumption of sphericity. Following each ANOVA, paired-samples t-tests were used in planned contrasts comparing the response to pleasant images to the response to neutral images and the response to unpleasant images to the response to neutral images.

Concordance for MZ/DZ twins: Concordance for each component was examined for MZ and DZ twins separately, using both measures of intersubject agreement (i.e., pearson's *r*) and score agreement (i.e., intraclass correlation; ICC). Subsequent estimates of heritability were based on ICC coefficients. Two-tailed *z*-tests were used to determine whether the MZ ICC significantly exceeds the corresponding DZ ICC.

Power: Previous studies demonstrating heritability of a variety of ERP components using MZ and DZ twins have used as few as 128-196 (Anokhin et al., 2010; Hall et al., 2006; Katsanis et al., 1997) and as many as 548 (Anokhin et al., 2008) individuals, suggesting the current sample size of 478 individuals should be sufficient to detect genetic contributions.

Identifying variability unique to emotion processing: Because the present proposal was primarily interested in identifying heritable neural indices of emotion processing, two separate methods were also used in order to isolate variance unique to processing of emotion. First, difference scores (i.e., pleasant minus neutral and unpleasant minus neutral) were calculated for each subject. Second, for each component scored, two regressions were conducted; one predicting the response to pleasant images from neutral images and one predicting the response to unpleasant images from neutral images. Standardized residuals representing variance

unique to the response to emotional images, after controlling for the response to neutral images, were saved for each subject and from each regression. Pearson's *r* and ICC for MZ and DZ twins, as well as estimates of heritability and environmental influence, were then calculated for the difference scores and the residual scores. Two-tailed *z*-tests were used to determine whether the MZ ICC significantly exceeded the corresponding DZ ICC.

Relationship to Self-Report: Pearson's *r* was used to explore the relationship between each component and continuous measures of self-reported TF and BI. Multiple regressions were also used to examine the unique, independent, or interactive nature of the relationship of the self-report domains to neural response. Finally, mixed-model ANOVAs were used to examine the interaction of TF and BI on patterns of emotional modulation.

Power: Even in very large unselected samples (e.g., >1,000; Hicks et al., 2006), correlations between self-reported phenotypes and physiological response are frequently small (.3 or lower; e.g., Benning et al., 2005; Hall, Bernat, & Patrick, 2007; Hicks et al., 2006). Nonetheless, the present sample size of 479 conferred power greater than .80 (two-tailed) to detect even small effects (i.e., r=.10; Lenth, 2006-2009).

Exploratory Analyses: I also conducted several exploratory analyses aimed at delineating the dynamics of emotion processing across the time-course of picture viewing. In addition to studying the interactive nature of the relationship between self-report domains and neural response (i.e., what does the neural response to threat look like in individuals high on TF and high on BI?), I also used multiple regression and tests of moderation to examine whether the relationship between early and late components is moderated by either of the self-report domains. For instance, early vigilance for emotional material, indicated in enhanced early ERP components, might be followed by a—and relate to—failure to engage in elaborative processing,

as indicated by a reduced LPP to this material, but only in individuals high on TF, consistent with a vigilance-avoidance model of anxiety (Weinberg & Hajcak, 2011a). On the other hand, in individuals low in BI, reduced early vigilance might also predict subsequent failure to engage in elaborative processing.

Biometric Modeling: All biometric modeling were conducted using MX statistical software.

I used biometric modeling to determine the heritability of each of the ERP components studied and the composite BI and TF Scores, as well as the genetic and environmental contributions to their covariance (Neale & Cardon, 1992). Biometric models partition phenotypic variance into three components: additive genetic (A), shared environmental (C), and nonshared environmental effects (E; this estimate also includes the contribution of measurement error). These models assume that shared environmental influences act identically on MZ and DZ twins, and thus that the genetic influence on the observed phenotype is additive in nature. Further assumptions are that no assortative mating occurs for the phenotype, and that there is no gene-environment interaction.

Because MZ twins are genetically identical, a correlation of 1.0 is observed for all genetic effects. DZ twins, in contrast, share an average of 50% of their genes, resulting in a correlation of .5 for all genetic effects. An MZ correlation that is twice as large as the DZ correlation suggests twin similarity is primarily due to additive genetic effects. However, when the DZ correlation is greater than half the MZ correlation, shared environmental factors should be contributing to the similarities between twins. Nonshared environmental effects represent influences (including measurement error) that contribute to *differences* between members of a twin pair, and so should be uncorrelated across members of both MZ and DZ twin pairs.

Biometric modeling will allow me to determine whether all or only some of these etiologic sources contributed to observed (phenotypic) variance in the ERP components or the self-report measures. Furthermore, this type of modeling permits the specification of the structure of covariance among the ERPs and self-report measures that is attributable to these relevant etiologic sources. I used the Cholesky decomposition method (Hicks et al., 2006; Neale & Cardon, 1992) to identify relevant sources of etiologic variance in the individual measures (i.e. additive genetic, shared environmental, and/or non-shared environmental) and to estimate genetic and environmental correlation matrices (i.e. patterns of relations among the genetic or environmental components of the differing scales).

This method is less restrictive than other biometric models, in that it does not impose a structure on the etiologic effects. This is particularly useful for a design of this type, in that twin pairs are measured on multiple phenotypes and ERP components. The Cholesky method fits a model to all calculable variances and covariances (i.e. cross-twin, within-trait variances and covariances; cross-twin, cross-trait variances and covariances), providing for decomposition of phenotypic covariances into genetic and environmental covariances and estimation of genetic and environmental correlations among all available measures. This allows for the evaluation of the structure of covariance that can be attributed to each etiologic source.

Results

Modulatory Effects of Picture Valence on EPN and LPP Response

Table 1 presents average score values by valence condition for the EPN and for each LPP score in the sample as a whole, and for MZ and DZ twin subsamples separately. Figures 1 and 2 present topographic maps for the EPN and LPP across all participants, depicting voltage differences (in μV) across the scalp for pleasant minus neutral pictures, and for unpleasant minus

neutral pictures. Grand average stimulus-locked ERP waveforms for the EPN (at scalp site Oz) and the LPP (at sites Pz and Fz) are also presented in Figures 1 and 2, respectively. Analysis of variance results, highlighting emotion-modulation effects for each ERP variable, are presented in Table 2.

Confirming patterns evident in Table 1 and Figures 1 and 2, scores for each ERP variable differed significantly by picture type, with both pleasant and unpleasant scenes eliciting larger amplitude responses than neutral scenes. Of note, the P300 scored at scalp site Pz between 300 and 600 ms, and the LPP between 600 and 1,000 ms, displayed the most robust effects of emotion (pleasant/unpleasant > neutral). In later time-windows, emotional modulation was diminished though not absent, at both Pz and Fz.

Reliability of ERP components

Split-half reliability estimates for ERPs in each time-window and at each electrode site are presented in Table 3. Reliability estimates for the residual scores for the emotional-neutral differences are presented in Table 4, and estimates for the difference scores (emotional minus neutral) are presented in Table 5. In these analyses, the clinical utility of a measure was considered to be unacceptable for values below .30, modest for values between .30 and .50, acceptable for values between .50 and .69, moderate for values of .70-.79, good for values of .80-.89, and excellent for values of .90 and above (Cicchetti, 1994). As can be seen Table 3, the ERPs themselves are acceptable-to-moderately reliable (i.e., split-half correlations ranged from .62 to .79), up to approximately 1,000 ms, at Oz, Pz, and Fz. After 1,000 ms, reliability decreases at both Pz and Fz (*r*s range from .10 to .64), though in most instances remains acceptable. The emotion residuals are in many instances across the time window also acceptably reliable. As shown in Table 4, the highest reliabilities for the residuals were at Pz, between 300 and 1,000 ms

(*r*s range from .31 to .43). In terms of the difference scores, reliability was notably decreased and unacceptable across the full time-window, with a maximum split-half correlation of .28 (at electrode Pz, between 600 and 1,000 ms), as indicated in Table 5.

MZ/DZ Twin Concordances and Heritability Estimates

Self-report. Table 3 displays Pearson's and ICC coefficients for self-reported TF and BI for MZ and DZ twins, respectively, as well as results of Z-score tests of differences between the two and ACE estimates. TF showed significant heritability, such that approximately 50% of the variance in this measure was explained by additive genetic influence, and 33% explained by nonshared environmental influences. BI was likewise subject to genetic influence, albeit with slightly lower heritability estimates (.34).

ERP response magnitude. Table 3 displays Pearson's and ICC coefficients for ERP components for MZ and DZ twins, respectively, as well as results of Z-score tests of differences between the two and ACE estimates for each ERP variable. Though MZ as compared to DZ twins tended to show higher concordance of electrocortical response across the time-course of affective picture processing (beginning in the time-window of the EPN), this effect was most pronounced—and consistently significant across all picture types—for the P300 during the 300 to 600 ms time window at scalp site Pz. Heritability estimates for the P300 during this time window ranged from .45 for the P300 elicited by neutral pictures, to .55 for the P300 elicited by pleasant and unpleasant pictures. The corresponding heritability results in this time-window at Fz were weaker, with the MZ/DZ difference achieving significance only for unpleasant pictures. The LPP to pleasant and neutral pictures during the 600 to 1,000 ms window also appeared heritable at scalp site Pz, as did later, frontal (Fz) modulation of the LPP by unpleasant pictures (between 1,000 and 3,000 ms).

Affective Modulation of ERPs. Table 4 shows that, after controlling for responsiveness to neutral pictures, as captured by emotional-neutral residuals, the P300 elicited by unpleasant pictures between 300 and 600 ms was heritable at both Pz and Fz. The corresponding modulatory effect for pleasant scenes fell just short of significance. Additionally, residual variance in the LPP for unpleasant scenes during the 1,000-2,000 ms and 2,000-3,000 ms windows (i.e., after controlling for the corresponding LPP elicited by neutral pictures) also emerged as heritable at the frontal (Fz) recording site. Notably, no evidence was found for heritability of emotional modulation of the EPN, either for pleasant scenes or unpleasant scenes.

Table 5 displays heritability estimates for affective modulation as measured by subtraction-based difference scores. In comparison to the residual-based differences, subtraction-based difference scores appear less subject to genetic influence. Indeed, here the only significant genetic contribution was to activity at electrode Fz, between 1,000 and 3,000 ms. However, the reduced reliability of these measures makes interpretation of this effect more difficult.

Relationship of ERPs to Self-Report

TF and BI were not significantly correlated with one another, suggesting the two represent independent dimensions (r=-.07, p>.18). Table 6 displays correlations between ERPs and self-reported TF and BI, for the full sample, and for Mz and Dz twins separately. As a reminder, high scores on the ESI reflect *low* levels of BI; negative correlations therefore suggest that low levels of behavioral inhibition relate to decreased ERP response. For presentation purposes, a median split was conducted on each of these two scales, and the waveforms at Pz and Fz for individuals high and low on TF and high and low in BI are presented in Figures 3 and 4. Correlations with self-report were strongest at Pz between 300 and 600 ms. Specifically, higher TF was associated with significantly larger P300s to both pleasant and unpleasant images, as

well as a greater difference between neutral and unpleasant images, as measured by the correlations with residual scores. The association with pleasant residuals was in the same direction and of a similar magnitude, though not significant. Low levels of BI, on the other hand, were associated with a smaller difference between neutral and pleasant images (as indexed by residual scores); associations with unpleasant residuals were again in the same direction and of a similar magnitude.

Significant associations also emerged between 600 and 1,000 ms, though only for the association with residuals. High TF was associated with enhanced responses to both pleasant and unpleasant images in this time-window, at both Pz and Fz. And, as above, low BI was associated with decreased response to both pleasant and unpleasant images, though these effects were strongest at Pz.

Multiple regressions predicting neural activity in this same time-window from both TF and BI indicated that these were independent and non-interactive effects, as shown in Table 7. TF and BI did not interact significantly to predict the magnitude of the P300 to pleasant or unpleasant images, nor to pleasant or unpleasant residuals (all *p*s>.25).

However, another possibility is that TF and BI do not interact to predict the response to any individual picture type, but rather the overall pattern of emotional modulation. In order to explore this, a median split was conducted on both TF and BI, creating a group high and low on each. A third variable was then constructed, identifying four groups: those low on TF and Low on BI; those low on TF and high on BI; those high on TF and low on BI; and those high on TF and high on BI. Nine 3 (picture type: pleasant, neutral, and unpleasant) x 4 (Low BI/Low TF; Low BI/High TF; High BI/Low TF; High BI/High TF) mixed-model repeated measures ANOVAs were then conducted (i.e., one for each component scored). The full results are

depicted in Table 8, and in the waveforms depicted in Figure 5; as indicated, TF and BI together did predict the pattern of affective modulation at electrode Pz, between 300 and 2,000 ms, as well as at Fz between 600 and 1,000 ms. Means for each group and picture type across these time windows are shown in Figure 5 and Table 9, along with results of independent t-tests exploring group differences (*p*-values Bonferroni adjusted for 6 contrasts for each component and valence type to .05/6= .008). As indicated in Figure 5, the ways in which the interaction of these traits became evident shifted across the time-course of the LPP. In the time-window of the LPP (at Pz, between 300 and 600 ms), the interaction between affective modulation and group was driven by contrasts between two groups: individuals low on BI and low on TF, who appeared to be characterized by a relatively flat pattern of emotional modulation (i.e., the response to both pleasant and unpleasant were relatively blunted relative to neutral images), and individuals high on BI and high on TF, who appeared to be characterized by *increased* modulation of the P300 by affective images.

Between 600 and 1,000 ms, at both Pz and Fz, however, it appeared that the low BI/low TF group differed most significantly from the other three groups, and continued to show a flattened pattern of emotional modulation.

Multivariate modeling to explore genetic contributions to associations between self-report and ERPs.

Tables 10 and 11 display fit statistics for ACE, AE, CE, and E models attempting to account for genetically- and environmentally-influenced covariance between trait fear and behavioral inhibition and activity in the time-window of the P300. I focused the analyses on this time-window because of a) the evident heritability of activity in the time-window of the P300, as well as affective modulation of this component, and b) the modest correlations with self-report in this

time-window. Akaike's information criterion (AIC = χ^2-2df; Akaike, 1987) was used to identify the best-fitting model in each instance. AIC balances goodness-of-fit with number of estimated parameters, identifying the most optimal model as the one where observed variances and covariances are reproduced with the greatest degree of parsimony (i.e., invoking the lowest number of unknown, estimated parameters possible). In comparative terms, a lower AIC indicates a better fit. As indicated in Tables 10 and 11, the best-fitting model to explain covariance between the P300 and self-report was in each instance an E-only model. This suggests that, though TF, BI, and the affect-modulated P300 are each heritable, non-shared environmental factors exert a greater influence over the associations between them than genetic factors.

Exploratory Analyses

Correlations among early and late ERP components are displayed in Table 12. As indicated, the magnitude of the EPN was related to the magnitude of later components across the time-window of the LPP. However, none of the exploratory analyses proposed—looking at moderating effects of TF or BI on the association between early and late ERPs—elicited significant results. In each instance, the magnitude of the EPN predicted the magnitude of the later LPP components within valence categories, but this relationship was not impacted by levels of TF or BI.

Discussion

Psychiatric disorders are the most common and costly forms of disease and injury worldwide. Despite this, our ability to accurately identify and treat these disorders is limited, due in part to the incredible complexity of the disorder categories themselves (Clark et al., 1995; Kessler et al., 2005; Krueger & Eaton, 2010; Krueger & Markon, 2006; Mineka et al., 1998; Watson, 2005). Furthermore, though psychiatric disorders are often assumed to be rooted in

some core dysfunction of neural circuitry (France et al., 2007; Leshner, 1997), it has been difficult to consistently map neural functioning on to the psychological functioning of the heterogeneous collections of individuals contained in any diagnostic category (Miller, 2010; Miller et al., 2007; Poldrack, 2010).

Rather than linking brain activity to complex disorders, therefore, there is increasing effort to refine current diagnostic systems by linking direct measures of biological and physiological systems to intermediate constructs— specific deviations in behavior and thought, measured continuously, which may underlie multiple disorders (e.g., Carter & Barch, 2007; Cuthbert & Insel, 2010; Insel et al., 2010; Patrick, Durbin, et al., 2012; Sanislow et al., 2010). In this vein, the current study aimed to identify genetically-influenced neurobehavioral traits—individual differences evident in both self-report and neural response—that might help improve classification and treatment of psychological dysfunction. Specifically, this study examined genetic contributions to multiple emotion-elicited Event Related Potentials (ERPs), as well as the link to the neurobehavioral traits of behavioral inhibition and trait fear, two constructs which are thought to cut across multiple psychiatric disorders (Barlow, 2004; Kramer et al., 2012; Patrick, Durbin, et al., 2012).

Reliability

Because I proposed to examine emotion-elicited ERP components as neural markers of neurobehavioral traits, the first step in the current study was to examine whether these neural responses might themselves be trait-like. One means of assessing this is to examine the reliability of the ERP components; high reliability suggests that these ERP components might be stable indices of affective response (Segalowitz & Barnes, 1993). Moreover, in order for a measure to be clinically-useful, between-subject variance cannot be exceeded by within-subject variance.

The validity of any individual difference measure therefore hinges on its reliability, or the tendency of that measure to reflect an individual's "true" scores, rather than measurement error (Cronbach & Meehl, 1955). Thus, the present study examined the reliability of the ERP measures collected (i.e., the EPN and each time-window of the LPP), focusing specifically on split-half reliability.

The split-half reliability of early ERP components (i.e., prior to 600 ms) was acceptable to moderate in each valence category, ranging from .67 to .79. While not achieving standards of excellence established in self-report literature, these estimates are higher than those found in other studies assessing split-half reliabilities of ERPs in order to establish them as clinically-useful measures (e.g., Segalowitz & Barnes, 1993). Values of this magnitude suggest that these early components can be reliably elicited across the course of a task, and are likely appropriate measures in studies concerned with individual differences.

Between 600 to 1,000 ms, reliability dropped somewhat, though was still largely in the acceptable range (i.e., between .62 and .74), but following 1,000 ms, reliability was markedly lower, ranging from .10 to .64, suggesting the intra-individual magnitude of the sustained affect-modulated LPP is much more variable following 1 second of picture viewing. Given the presumed functional distinctions between early and late ERP components, this suggests that the degree of early, relatively obligatory attentional capture is more stable and trait-like, whereas ongoing elaborative processes reflected in the sustained LPP might be more influenced by situational variables and the content of specific images.

However, it is also possible that this sustained waveform reflects the activity of multiple diverse components which were not well-captured by the broad time-windows selected for the present study (e.g., Foti et al., 2009; Weinberg & Hajcak, 2011b). Likewise, there is evidence

that measurement of this sustained waveform is more sensitive to noise and error (e.g., the measurement of this slow-wave activity will depend more on selection of filter settings; Hajcak et al., 2012), and the 30 trials per condition used in the present study (15 per half) may have been insufficient to maximize signal-to-noise ratio. Future studies might examine this in a paradigm with increased number of trials used per condition. Finally, the specific pictures used within each broad picture category were quite varied, and represented a wide array of contents (e.g., erotic, exciting, and affiliative within the pleasant category); future studies focusing on larger numbers of pictures drawn from more homogenous subcategories might find evidence for increased reliability estimates of ERPs across the time-course of picture processing.

In addition to examining the reliability of the ERP components elicited by each picture category, I also looked at the reliability of two different methods for quantifying affective modulation of these components: 1) Difference scores, in which the ERP to neutral images was subtracted from the ERP elicited by either pleasant or unpleasant images, and 2) Standardized residual scores, representing variance unique to the response to emotional images, after controlling for the response to neutral images. Reliability estimates for residual scores, while not as high as scores for the components themselves, were notably higher than estimates for difference scores (particularly between 300 and 1,000 ms at Pz, where estimates ranged from .25 to .43 for residuals, compared to .14 to .28 for difference scores), suggesting that residual scores represent a more reliable method of capturing individual differences in affective modulation than difference scores.

This is consistent with evidence that methods relying on differences between averages are somewhat ineffective in isolating variance unique to emotional images in that the resulting difference score remains correlated with both initial values (i.e., the average response to neutral

and average response to emotional images); thus the difference cannot be said to uniquely reflect activity associated with emotional processing (Cronbach, & Furby, 1970; DuBois, 1957). Residuals are also a difference score of sorts, but instead reflect the difference between an individual's observed average response to emotional images and the average that would be predicted from their neutral average; these residuals will be independent from the average response to neutral images, but correlated with the average response to emotional images. Residuals thus more successfully capture unique variance associated with emotional responding (Cronbach & Furby, 1970; DuBois, 1957; Traub, 1967), and may be a more reliable means of measuring affective modulation. However, future research seeking to increase reliability of the raw components might also provide more clarity to this issue.

Heritability

Consistent with previous reports, the self-reported domains of trait fear (Kramer et al., 2012) and behavioral inhibition (Krueger et al., 2007) were both significantly heritable. Heritability estimates for trait fear were comparable to those observed in previous reports using much larger samples (Kramer et al., 2012). On the other hand, heritability estimates for behavioral inhibition were somewhat lower than previously observed (Krueger et al., 2002), and also somewhat lower than estimates for trait fear. However, it should be noted here that trait fear was more normally distributed in the present sample, with extremes at both ends well-represented, allowing for more accurate estimation of genetic contributions to this self-reported trait. The scores for behavioral inhibition, on the other hand, while still normally distributed, had a less dense representation in the extreme range of behavioral disinhibition. Future studies seeking to replicate this work might selectively sample from the population for extremes in both trait fear and behavioral inhibition/disinhibition. Nonetheless, given that each of these

dimensions has also been identified as a correlate of multiple forms of psychopathology, the present results confirm prior evidence that the two dimensions are subject to genetic influence, and may represent viable targets for ongoing neurobiological research into dimensions of psychopathology (Insel et al., 2010; Sanislow et al., 2010).

The present study also sought to examine the contribution of genetic influences to multiple ERP components elicited by pleasant, neutral, and unpleasant picture stimuli. Consistent with previous work (Cuthbert et al., 2000; Foti et al., 2009; Hajcak et al., 2012; Olofsson et al., 2008), robust emotional modulation of ERP components was evident across the time-course of emotional picture processing, beginning as early as 175 ms and continuing up through 3 s following picture onset. However, there were important differences in the genetic contributions to different components, as I discuss below.

Heritable Aspects of ERP Responses to Picture Stimuli

I first considered the degree to which differing ERP components demonstrated heritability for pictures of each type (pleasant, neutral, unpleasant). Across picture types, the strongest and most consistent evidence of heritability was found for the centro-parietal P300 component observed between 300 - 600 ms. For this component, MZ twin correlations significantly exceeded DZ twin correlations for pictures of each type—indicating significant heritability for each. The finding of robust heritability for the P300 response to affective and neutral picture stimuli is consistent with previously reported evidence for a substantial genetic contribution to the non-affective P300 elicited in oddball tasks (Carlson & Iacono, 2006; Hall et al., 2006; Katsanis et al., 1997), as well as with previous evidence from affective facial stimuli (Anokhin et al., 2010). Indeed, the present data suggest that genes account for between 45 and 55% of variance in this component overall, which is comparable to previous reports of genetic contributions to personality trait

characteristics (e.g., Blonigen, Hicks, Krueger, Patrick, & Iacono, 2005; Jang, Livesley, & Vemon, 2006; Jang, Livesley, Vernon, & Jackson, 2007). Thus, the magnitude of the picture-elicited P300 may represent a heritable trait-like index of stimulus processing.

In contrast, evidence for a genetic contribution to the EPN, presumed to reflect a more obligatory neural response associated with early perceptual registration, was more equivocal. Though for pictures of all types the correlation for MZ twins exceeded that for DZ twins, the difference in correlation values only reached significance for unpleasant images. However, the fact that MZ/DZ correlation differences for pleasant and neutral pictures were only somewhat lower than for unpleasant, together with the fact that the heritable effect for unpleasant pictures was rendered null by controlling for its overlap with neutral picture EPN (see below), suggests that more compelling evidence of heritability of the EPN might well emerge for pictures of other types in samples of larger size.

Additionally, the present study is the first to demonstrate genetic contributions to later, more frontal, ERP components. Specifically, for the LPP between 2,000 and 3,000 ms, there was evidence of heritability for the response to both pleasant and unpleasant scenes, at scalp site Fz. Previous reports of an anterior shift in the distribution of the LPP over the course of picture presentation have suggested that this more frontal component reflects continued stimulus engagement and semantic elaboration (Hajcak et al., in press; Hajcak, MacNamara, et al., 2010; Hajcak & Olvet, 2008; Hajcak et al., 2012; MacNamara et al., 2009; Olofsson et al., 2008). The implication is that the extent of this later elaborative processing is also subject to genetic influence; the question of whether this influence may be specific to emotional content is discussed below.

Heritable Aspects of Affective Modulation of ERP Components

Whereas a previous report demonstrated genetic contributions to amplitude differences in ERPs elicited by *affective visual stimuli* (Anokhin et al., 2010), the present study provides the first evidence for a significant genetic contribution to *affective modulation*, measured via residual scores, of ERPs to visual stimuli (i.e., the degree to which affective visual stimuli elicit larger ERPs than neutral stimuli). In particular, modulation of the P300 elicited by unpleasant scenes (i.e., the systematic variance in response to scenes of this type distinct from response to neutral scenes) was found to be modestly heritable. A trend-level effect for heritability of the P300 to pleasant versus neutral scenes was also evident for the 300-600 ms time window. Together, these results suggest that arousal-related increases in the P300 are in part heritable—and by extension, that this affect-modulatory effect might serve as an indicator of genetically-transmitted variation in sensitivity to affective visual stimuli. From this perspective, the emotion-modulated P300 may hold potential as tool for the study of individual differences in early motivated attention (cf. Lang et al., 1997).

Results for residual scores for the later, more frontal LPP were more equivocal. While the MZ correlation exceeded the DZ correlation for the response to unpleasant versus neutral images at Fz between 1,000 and 3,000 ms, heritability estimates were modest. Nonetheless, model-based evidence for genetic influence specific to affective processes was evident for the full (non-residualized) late LPP scores. In particular, between 2,000 and 3,000 ms at scalp site Fz, there was evidence for genetic contributions to responses for both pleasant and unpleasant pictures, but not neutral. The implication is that later, more frontal neural activity is somewhat heritable, but perhaps only in the context of processing affective images. Further research will be necessary to corroborate and clarify this possibility.

In contrast, evidence for heritability of affective modulation measured by subtraction-based difference scores is quite limited. This is likely due at least in part to the low reliability of these scores, as discussed above. Because evidence for both the reliability and heritability of difference scores was lacking, they were not included in subsequent analyses, reported below.

Though the current sample was large for an ERP study, it is modest in comparison with many studies that have used biometric modeling. Some of the marginal effects evident in the current work (e.g., evidence for heritability of the EPN across picture categories, or for affective modulation of the P300 by pleasant pictures) might well emerge as significant given increased statistical power in a larger sample.

In the present work, the strongest and most consistent evidence of heritability was found for the centro-parietal P300 component, consistent with previous studies demonstrating substantial heritability of the target-elicited P300 (Eischen & Polich, 1994; Hall et al., 2006; Iacono et al., 2003; Katsanis et al., 1997; Polich & Bloom, 1999). This raises the question of whether the evidence for heritability in the affective viewing paradigm observed here reflects specific genetic influences on affective processing or instead general genetic influences on target processing. Because our study utilized a passive viewing paradigm, it is difficult to say definitively. Future studies in which target status and valence are fully crossed (e.g., Ferrari et al., 2010; Weinberg, Hilgard, et al., 2012) will be needed to resolve this question. However, the evidence reported here for modest heritability of affective processing even after controlling for activity related to neutral images suggests some specificity of genetic contributions to emotion-related increases in the P300.

However, it is also worth noting that the estimates of genetic contributions to affective modulation of the P300 were more modest than those observed for the raw components. For

example, in the 300 to 600 ms time-window, estimates of additive genetic contribution to processing of neutral, pleasant, and unpleasant images ranged from .45 to .55, whereas for modulation of the P300 by unpleasant images the estimate of heritability was .29. This may in part be due to the use of residual scores: While potentially preferable methodologically to subtraction-based difference scores, residuals likely still represent an imperfect method for isolating variance unique to affective processes (Cronbach & Furby, 1970; DuBois, 1957; Traub, 1967), and, as noted above, were less reliable than the raw components. Moreover, in either case, the use of neutral images as a non-affective comparison carries risks. For example, there is increasing evidence that arousal-related processes may be evident in the response to neutral images (e.g., Ferri, Weinberg, & Hajcak, 2012; Ito & Cacioppo, 2000; Weinberg & Hajcak, 2010). That is, the ERP response to neutral pictures may not represent a pure 'baseline'. Thus, factoring out variance in common with responsivity to purportedly neutral images may result in a dilution of affect-related variance. Nonetheless, the current heritability estimates are comparable to those in other published research (e.g., Anokhin et al., 2008; Anokhin et al., 2010), and even modest evidence for heritability of affective processing provides an impetus for further research along these lines.

Additionally, significant genetic contributions to emotional processing were most consistently observed for responses to unpleasant scenes. This might suggest specific genetic contributions to processing of unpleasant or threatening material, consistent with the notion that such material is more biologically-relevant and motivationally-salient than pleasant content (i.e., a negativity bias; Ito et al., 1998). Processing of biologically-salient material might also be more subject to selection pressures. However, we would caution against this interpretation. For one thing, the effects for pleasant pictures, although not significant, were consistently in the same

direction and of similar magnitude as those for unpleasant scenes. Additionally, the pleasant category included a subset of exciting/sports scenes (i.e., action), which are known to elicit ERP responses on par with neutral images (Briggs & Martin, 2009; Weinberg & Hajcak, 2010). Inclusion of these exciting scenes may have diluted ERP responses to the pleasant category, making the results—particularly results concerning variance in pleasant picture response distinct from response to neutral scenes—somewhat more difficult to interpret. Inclusion of these scenes may also have contributed to the finding that unpleasant images elicited higher arousal ratings and larger LPPs than pleasant images, which might result in more reliable measurement. Future work could address this point by directly examining genetic contributions to ERPs elicited by pleasant and unpleasant picture stimuli equated for biological relevance (e.g., erotic and threat/mutilation images; Briggs & Martin, 2009; Weinberg & Hajcak, 2010; Weinberg, Hilgard, et al., 2012).

Associations with self-reported Trait Fear and Behavioral Inhibition

A primary goal of this study was to examine the association between self-reported affective styles—trait fear and behavioral inhibition—and the emotion-modulated P300/LPP, in service of establishing the LPP as a reliable and heritable means of capturing these latent traits. The results of the present study suggest that both self-reported trait fear and behavioral inhibition relate to the magnitude of emotional response. Individuals reporting high levels of trait fear were characterized by an enhanced P300 to both pleasant and unpleasant images, while individuals reporting low levels of behavioral inhibition displayed the opposite pattern: attenuated responses to both pleasant and unpleasant images. This effect was similar in the association with affective modulation (i.e., the difference between emotional and neutral images, as captured by residual scores). Here, high trait fear appeared to be more strongly associated with an enhanced response

to unpleasant images (compared to neutral), but the effect was in the same direction for pleasant images. Likewise, behavioral disinhibition appeared to be more strongly associated with a decreased response to pleasant images, but the effect for unpleasant images was in the same direction and in later time-windows was also significant.

The results for trait fear are consistent with previous studies indicating individuals diagnosed with anxiety disorders frequently display an enhanced P300, including spider-phobic individuals viewing spider pictures (Leutgeb et al., 2009), socially-phobic individuals viewing angry and fearful faces (Moser et al., 2008; Mühlberger et al., 2009), panic disorder patients viewing body-related words (Pauli et al., 1997), and individuals with Generalized Anxiety Disorder (GAD) viewing unexpected threat images (Weinberg & Proudfit, in prep). This suggests that individuals high on trait fear allocate increased attentional resources towards threatening images, even in a passive viewing task, in which increased attention is neither necessary nor necessarily adaptive. Moreover, these data are consistent with evidence that high levels of trait fear are associated broadly with greater tonic activation of the defensive motivation system, including increased amygdala activity (Dilger et al., 2003; Stein et al., 2002), greater fear-potentiated startle (Cook et al., 1991; Cook III et al., 1992; Corr et al., 1997; Corr et al., 1995; Vaidyanathan et al., 2008), and larger skin-conductance responses (Roth et al., 1990; Weerts & Lang, 1978).

This pattern of maladaptive increased attention to threat might play an important role in the development and maintenance of multiple anxiety disorders, as increased attention to threat could result in increased likelihood of detecting threat. Moreover, a lower threshold for the detection of threat, as well as chronic and protracted activation of the defensive system, is

thought to represent a vulnerability marker for multiple forms of internalizing disorders (Patrick & Bernat, 2010; Rosen & Schulkin, 1998).

On the other hand, these findings also demonstrate that individuals low in trait fear are characterized by *decreased* attention to threatening stimuli. Individuals who fall at the low end of this dimension tend to be characterized by interpersonal boldness, thrill-seeking, and a relative immunity to stress (Kramer et al., 2012; Vaidyanathan et al., 2008), and low trait fear has been linked to decreased amygdala response (Blair, 2008; Blair et al., 1999; Mitchell et al., 2006; Patrick, 1994), an absence of normal patterns of startle potentiation (Benning et al., 2005; Patrick, 1994; Patrick et al., 1993; Vaidyanathan et al., 2011; Vaidyanathan et al., 2008), and a blunted electrodermal response (Hare et al., 1978; Lorber, 2004). Decreased attention to threatening stimuli, as reflected in the attenuated P300, might relate to all of these phenomena.

Combined, this evidence suggests that the trait dimension of fear/fearlessness reflects individual variability in the propensity to activate the defensive motivation system, and that the P300/LPP response to threatening images might be a useful measure of this trait. The present results therefore provide support for the inclusion of the emotion-modulated P300/LPP as a unit of measurement in future studies seeking to measure the latent construct of trait fear. However, the marginal effects for the association between trait fear and modulation of the P300 by pleasant images suggests trait fear may not only be characterized by abnormal reactivity to threat—indeed, it is possible that trait fear may relate to arousal-related increases in attention more broadly (Aldao & Mennin, 2012; Mennin, Heimberg, Fresco, & Ritter, 2008; Mennin, McLaughlin, & Flanagan, 2009; Weinberg & Hajcak, 2011a; Weinberg, Perlman, Kotov, & Proudfit, in prep). Future research using more stimuli might systematically vary valence and arousal levels to better understand this.

Behavioral disinhibition, on the other hand, was linked to decreased emotional response from 300 to 1,000 ms, contrary to my hypotheses that individuals on the high end of this dimension would primarily exhibit deficits in sustained attention, as reflected in activity beyond 1,000 ms. Nonetheless, these results are consistent with some prior evidence that individuals characterized by behavioral disinhibition often display a decreased response to standardized emotional stimuli (Dunning et al., 2011). Moreover, the flip side of these findings is that those individuals characterized by relatively higher levels of behavioral inhibition exhibited increased LPP/P300s to both pleasant and unpleasant stimuli, consistent with evidence that behavioral inhibition relates to hypersensitivity to multiple types of stimuli (Fox, 1989; Fox, Henderson, Marshall, Nichols, & Ghera, 2005). Both hyper- and hypo-sensitivity to emotional material related to behavioral inhibition might also subsequently serve as a vulnerability marker or even a mechanism for the development of multiple forms of psychological dysfunction (e.g., Hill, Degnan, Calkins, & Keane, 2006; Pérez-Edgar et al., 2010). Future longitudinal studies might examine this further. Nonetheless, the results of this study suggest that future studies might seek to incorporate the emotion-modulated P300 into batteries of tests seeking to assess the latent traits of both trait fear and behavioral inhibition.

Though the effects described above indicate that trait fear and behavioral inhibition relate in similar ways to the magnitude of emotional response, the two dimensions are not correlated with one another, and the results of the regression analysis suggest the two effects on the P300/LPP are independent of one another. While this is consistent with a burgeoning movement to examine linear associations between physiology and dimensions of human behavior (Cuthbert & Insel, 2010; Insel et al., 2010; Sanislow et al., 2010), it is possible that the examination of interactions/additive effects of these dimensions might explain more about both

psychopathology and neural response (e.g., Weinberg, Kotov, & Proudfit, under review). Moreover, pathological patterns of response to emotions might emerge not from the response to any single picture type, but rather from patterns of emotional modulation, or the degree to which individuals differentiate stimuli of different types (e.g., Patrick, et al., 1993). To that end, I also examined the ways in which trait fear and behavioral inhibition might interact to predict emotional modulation of ERPs across the time-course of picture processing by looking at these responses in individuals high and low on each trait.

The largest effects were again observed in the 300-1,000 ms time-window. Consistent with the effects described above, in the time-window of the P300 there appeared to be an additive rather than interactive effect of behavioral inhibition and trait fear, such that the most pronounced differences were between those individuals who rated themselves as high on both trait fear and behavioral inhibition, and those who rated themselves as low on both trait fear and behavioral inhibition. Individuals high on both traits were characterized by increased modulation of the P300 by emotional stimuli of both types, relative to neutral, suggesting increased reactivity to more arousing stimuli in these individuals (Aldao & Mennin, 2012; Fox, 1989; Mennin et al., 2008; Pérez-Edgar et al., 2010; Weinberg & Hajcak, 2011a). On the other hand, individuals low on both traits were characterized by flatter patterns of emotional modulation, such that, though emotional modulation was still apparent in these individuals, the degree of differentiation between emotional and neutral stimuli was less (Patrick et al., 1993; Samimi Sadeh & Verona, 2012).

Following this, the main effect of behavioral inhibition appeared to exert more of an influence on emotional modulation than the effect of trait fear. Between 600 and 1,000 ms, Individuals low on behavioral inhibition differed from individuals high on behavioral inhibition,

regardless of the level of trait fear, though, again, this difference was most pronounced for those low on both behavioral inhibition and trait fear, suggesting some remaining influence of this additive effect.

Combined, these data suggest that recent attempts to describe psychological dysfunction in terms of dimensional systems (Cuthbert & Insel, 2010; Insel et al., 2010; Sanislow et al., 2010) might profit from the consideration of multiple systems simultaneously. Examining the interactive or additive effects of multiple traits and neural responses might in the end reveal more about mechanisms of dysfunction, and might help to refine our understanding of both the physiological and self-reported phenotype. Moreover, looking at the joint impact of trait fear and behavioral inhibition on neural response might be useful in identifying individuals at risk for psychopathology.

A few caveats are warranted regarding the above associations with self-report. First, given the limited reliability of the residual scores, all of the above findings linking individual differences with emotion modulation should be replicated in studies in which reliability of these measures has been increased, either via more trials, or more narrowly defined categories of stimuli. Additionally, though use of a community sample was a strength in several regards, the effect sizes are somewhat smaller than those observed in studies using clinical samples (MacNamara & Hajcak, 2009; Weinberg & Hajcak, 2011a; Weinberg & Proudfit, in prep). Yet even in very large unselected samples (e.g., >1,000; Hicks et al., 2006), correlations between self-reported phenotypes and physiological response are frequently small (.3 or lower; e.g., Benning et al., 2005; J. Hall et al., 2007; Hicks et al., 2006), suggesting the real size of effects in the population might be modest. Future studies should examine and attempt to replicate these

effects in large and heterogeneous clinical samples, as well as in individuals at *risk* for internalizing and externalizing disorders.

Additionally, the implications that these results have for bottom-up vs. top-down processing of emotional content are unclear. My initial hypotheses were that individual differences in behavioral inhibition would be more strongly reflected in later, more elaborative ERP components, suggesting variability in sustained attention. However, these hypotheses were not borne out. Instead, both trait fear and behavioral inhibition showed the strongest associations with activity between 300 and 1,000 ms. Given the reduced reliability of ERP components in later time-windows, however, it is difficult to know whether these associations are nonexistent, or whether the associations might instead be obscured by increased noise in the ERP signal. Future studies focused on increasing the reliability of this later LPP should also revisit its associations with trait fear and behavioral inhibition.

Genetic Overlap between self-report and ERP

The present study also sought to specify the genetic overlap between self-reported trait fear and behavioral inhibition and affective modulation of the P300. Consistent with prior research, (e.g., Kendler, Prescott, et al., 2003; Katsanis et al., 1997; Kramer, et al., 2012; Krueger et al., 2002; Young et al., 2000), the amplitude of the P300, self-reported behavioral inhibition, and self-reported trait fear were each significantly heritable. Moreover, as discussed above, there were associations between trait fear and behavioral inhibition and emotional modulation of the P300. However, contrary to my hypotheses, the association between the magnitude of the P300 and self-reported trait factors did not appear to be influenced by genetic contributions. Instead, each association appeared primarily attributable to non-shared environmental effects.

This suggests first that emotional modulation of the P300 is regulated by different genetic factors than those contributing to trait fear and behavioral inhibition. However, the results are still potentially informative. For instance, one possibility is that those genetically predisposed to emotional hyper- or hyporeactivity, as indexed by abnormalities in the modulation of the P300, and those who are *also* genetically predisposed to extremes in trait fear or behavioral inhibition might be particularly at risk for adverse psychological outcomes. Future studies might explore the possibility that the P300 and self-reported trait fear and behavioral inhibition might have additive or interactive effects in predicting the development of diagnoses over time, or prognosis for treatment.

Likewise, evidence that the association between the self-report and neural response domains is largely attributable to environmental factors suggests the need for future studies examining specific forms of environmental adversity that might account for this link (e.g., Hicks, DiRago, Iacono, & McGue, 2009). However, because estimates of non-shared environmental effects also include error, a final possibility is that the association between the P300 and trait fear and behavioral inhibition are the result of sampling error. The consistency of these results with prior research on fear and BI would argue against this, but future studies might seek to replicate these effects.

Conclusion

The present dissertation sought to identify links between self-report and neural response in service of identifying potential *neurobehavioral traits* (Depue & Iacono, 1989; Patrick & Bernat, 2010; Patrick, Durbin, et al., 2012). In particular, the present proposal aimed to identify genetic influences on emotion-modulated ERPs and to link these ERPs to the neurobehavioral

traits of behavioral inhibition and trait fear/fearlessness, two constructs which cut across multiple psychiatric disorders (Barlow, 2004; Kramer et al., 2012; Patrick, Durbin, et al., 2012).

The current results suggest heritability of individual differences in neural indices of emotion processing, both in terms of early, relatively obligatory allocation of attention and later, more elaborative processing. Moreover, these ERPs were related to both behavioral inhibition and trait fear. Given increasing contemporary interest in the neurogenetics of psychiatric disorders (Anokhin, Heath, & Myers, 2004; Bogdan, Hyde, & Hariri, 2012; Bogdan, Nikolova, & Pizzagalli, 2012; Cloninger, 1987; Cuthbert & Insel, 2010; Insel et al., 2010; Yates, 2012), these findings indicate that the P300 and sustained LPP might serve as useful intermediate phenotypes in research investigating neurobiological and genetic underpinnings of a range of neuropsychiatric disorders. Measures of this type are likely to be particularly valuable because multiple psychiatric disorders are characterized by abnormalities in emotion processing, whether in terms of maladaptive early attention (Li & Luo, 2005; MacNamara & Hajcak, 2009, 2010; Mogg, Bradley, Miles, & Dixon, 2004; Van Strien et al., 2009; Weinberg & Hajcak, 2011a), or deficits in sustained affective processing (e.g., Dunning et al., 2011; Foti et al., 2010; Franken, 2003; Levenston et al., 2000; Patrick et al., 1993; Weinberg & Hajcak, 2011a). Related to this, a wide array of psychiatric disorders display abnormalities in the magnitude of the emotion-modulated P300 and LPP, including phobias (Leutgeb et al., 2009; Moser et al., 2008; Mühlberger et al., 2009), panic disorder (Pauli et al., 1997), generalized anxiety Disorder (MacNamara & Hajcak, 2010; Weinberg & Hajcak, 2011a), depression (Foti et al., 2010), schizophrenia (Horan et al., 2010), and substance abuse (Dunning et al., 2011; Franken, 2003).

Furthermore, an extensive body of non-affective research using the oddball P300 documents a relationship between reduced P300 amplitude and externalizing disorders and

tendencies (e.g., Bernat et al., 2011; Brigham et al., 1995; Iacono et al., 2003, 2008) that appears to reflect shared genetic influence (Hicks et al., 2006). However, no work to date has explored how genetic contributions to *emotional* modulation of the P300 might be associated with pathological emotional responding. The current results, which identify genetically-transmitted variation in neural indices of emotional response that is linked to trait fear and behavioral inhibition, may therefore facilitate the identification of neurobiological markers for neuropsychiatric disorders. These data may therefore be useful in future studies aiming not only to better characterize current dysfunction, but also in future studies concerned with risk for and the development of psychopathologies.

Table 1. Means and standard deviations for ERP variables for all subjects (left columns) and for MZ and DZ twins separately (middle and right columns).

	All subjects		**MZ**		**DZ**	
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*
Trait fear	1.13	.47	1.14	.51	1.11	.42
Behavioral inhibition	.15	.12	.14	.12	.16	.13
EPN (175-275 ms) Oz						
Pleasant	1.55	4.77	1.62	4.73	1.48	4.82
Neutral	3.55	4.65	3.57	4.59	3.53	4.71
Unpleasant	2.21	4.90	2.29	4.83	2.13	4.98
P300 (300-600 ms) Pz						
Pleasant	10.18	5.62	10.37	5.57	9.99	5.68
Neutral	4.60	4.91	4.59	4.90	4.61	4.93
Unpleasant	10.98	5.83	11.00	5.94	10.96	5.72
P300 (300-600 ms) Fz						
Pleasant	2.71	7.29	2.99	7.43	2.41	7.15
Neutral	-2.69	6.51	-2.65	6.73	-2.72	6.29
Unpleasant	2.24	7.17	2.12	7.22	2.37	7.13
LPP (600-1000 ms) Pz						
Pleasant	7.36	4.74	7.37	4.54	7.36	4.95
Neutral	2.01	4.01	1.92	4.19	2.11	3.81
Unpleasant	9.59	5.32	9.54	5.05	9.64	5.60
LPP (600-1000 ms) Fz						
Pleasant	5.56	6.84	5.83	6.57	5.27	7.12
Neutral	.43	6.04	.32	6.26	.54	5.81
Unpleasant	6.41	6.98	6.46	6.88	6.35	7.10
LPP (1000-2000 ms) Pz						
Pleasant	3.24	4.18	3.36	4.06	3.11	4.30
Neutral	.78	3.38	.71	3.31	.86	3.46
Unpleasant	4.33	4.43	4.37	4.14	4.29	4.71
LPP (1000-2000 ms) Fz						
Pleasant	5.07	5.75	5.17	5.65	4.96	5.87
Neutral	2.69	5.04	2.49	5.10	2.90	4.98
Unpleasant	5.65	5.84	5.58	5.54	5.72	6.16
LPP (2000-3000 ms) Pz						
Pleasant	1.87	3.89	2.00	3.89	1.73	3.90
Neutral	.24	3.34	.21	3.41	.27	3.26
Unpleasant	2.12	4.13	2.07	3.93	2.18	4.33
LPP (2000-3000 ms) Fz						
Pleasant	4.71	5.19	4.90	5.38	4.50	4.99
Neutral	3.25	4.65	3.11	4.95	3.41	4.31
Unpleasant	4.26	5.39	4.20	5.08	4.32	5.70

Table 2. Analysis of Variance results for effects of emotion on each ERP variable, at relevant scalp sites

ERP	Time-Window/Scalp Site	Main Effect of Emotion *F* (2, 910)	η_p^2	Pleasant vs. Neutral *t*(455)	Unpleasant vs. Neutral *t*(455)
EPN	175-275 ms				
	Oz	195.66	.30	19.84	12.81
P300	300-600 ms				
	Pz	843.84	.65	33.68	33.86
	Fz	361.20	.44	24.17	22.60
LPP	600-1000 ms				
	Pz	857.61	.66	29.77	35.64
	Fz	307.63	.40	19.67	22.42
	1000-2000 ms				
	Pz	214.91	.33	14.38	19.30
	Fz	74.66	.14	9.05	11.72
	2000-3000 ms				
	Pz	58.52	.12	8.85	9.69
	Fz	15.69	.03	5.38	4.04

Note: $p<.001$ for all comparisons

Table 3. Split-half-reliabilities, twin concordances and heritability estimates for each self-report and ERP variable, by picture condition

Variable	Split-half	**MZ concordance**		**DZ concordance**		**Comparison**		**ACE estimates (90% CI)**		
	R	*r*	ICC	*r*	ICC	*Z*	*p*	A^2	C^2	E^2
Trait fear	-	.72**	.72	.32**	.32	**4.25**	**<.001**	.53 (.17-.74)	.14 (0-.47)	.33 (.25-.43)
Behavioral inhibition	-	.68**	.68	.50**	.51	**1.97**	**.04**	.34 (.22-.76)	.17 (0-.26)	.49 (.18-.69)
EPN (175-275 ms) Oz										
Pleasant	.76**	.50**	.50	.37**	.37	1.15	.12	.25 ($1.99e^{-15}$-.57)	.24 (0-.49)	.51 (.41-.64)
Neutral	.77**	.54**	.54	.42**	.42	1.12	.13	.16 ($1.29e^{-14}$-.49)	.36 (.08-.56)	.47 (.38-.59)
Unpleasant	.79**	.56**	.56	.35**	.35	**1.92**	**.03**	.35 (.03-.65)	.19 (0-.50)	.45 (.34-.59)
P300 (300-600 ms) Pz										
Pleasant	.75**	.59**	.58	.13	.13	**3.85**	**<.001**	.55 (.43-.65)	0 (0-.11)	.45 (.35-57)
Neutral	.67**	.46**	.46	.19*	.19	**2.21**	**.02**	.45 (.14-.56)	0 (0-.24)	.55 (.44-.68)
Unpleasant	.70**	.58**	.57	.24*	.23	**2.99**	**<.001**	.55(.29-64)	0 (0-.21)	.45 (.36-.56)
P300 (300-600 ms) Fz										
Pleasant	.78**	.41**	.40	.25*	.28	.98	.16	.28 (0-.51)	.11 (0-.40)	.61 (.49-.75)
Neutral	.69**	.44**	.43	.30*	.30	1.09	.14	.16 (0-.51)	.26 (0-.47)	.58 (.47-.71)
Unpleasant	.70**	.55**	.54	.28*	.31	**2.06**	**<.05**	.52 (.17-.64)	.03 (0-.32)	.45 (.36-.56)
LPP (600-1000 ms) Pz										
Pleasant	.63**	.37**	.37	.14	.13	**1.87**	**<.05**	.38 (.23-.51)	0 (0-.20)	.62 (.49-.77)
Neutral	.45**	.48**	.48	.16	.16	**2.62**	**<.05**	.43 (.30-.54)	0 (0-.30)	.57 (.46-.70)
Unpleasant	.63**	.33**	.33	.20*	.20	1.01	.15	.35 (0-.50)	.03 (0-.32)	.62 (.50-.78)
LPP (600-1000 ms) Fz										
Pleasant	.74**	.48**	.48	.18	.19	**2.40**	**<.05**	.49 (.28-.60)	0 (0-.15)	.51 (.40-.64)
Neutral	.62**	.36**	.37	.19*	.18	1.50	.07	.28 (.0-.47)	.06 (0-.36)	.66 (.53-.80)
Unpleasant	.63**	.44**	.47	.22*	.22	**2.07**	**<.05**	.47 (.34-.58)	0 (0-.25)	.53 (.42-.66)
LPP (1000-2000 ms) Pz										
Pleasant	.45**	.23**	.23	.21*	.22	.08	.47	.15 (0-.40)	.10 (0-.31)	.75 (.60-.89)
Neutral	.22**	.42**	.42	.21*	.21	**1.70**	**<.05**	.43 (.01-.55)	0 (0-.25)	.57 (.45-.70)
Unpleasant	.43**	.15	.15	.09	.09	.45	.32	.17 (0-.32)	0 (0-.19)	.83 (.68-.99)
LPP (1000-2000 ms) Fz										
Pleasant	.64**	.39**	.39	.39**	.39	0	n/a	.18 (0-.52)	.25 (0-.46)	.57 (.45-.71)
Neutral	.44**	.32**	.33	.24**	.24	.71	.24	.16 (0-.46)	.16 (0-.37)	.68 (.54-.82)
Unpleasant	.44**	.30**	.35	.19**	.15	1.56	.06	.33 (0-.46)	0 (0-.28)	.67 (.55-.81)
LPP (2000-3000 ms) Pz										
Pleasant	.33**	.25**	.25	.12	.13	.90	.19	.25 (0-.40)	0 (0-.29)	.75 (.59-.92)
Neutral	.11*	.32**	.32	.28**	.28	.32	.38	.09 (0-.46)	.23 (0-.41)	.69 (.53-.83)
Unpleasant	.17**	.17*	.17	.22*	.22	.39	.34	.02 (0-.37)	.16 (0-.30)	.82 (.63-.96)
LPP (2000-3000 ms) Fz										
Pleasant	.59**	.24**	.24	.29**	.29	-.39	.35	0 (0-.36)	.26 (0-.38)	.74 (.62-.87)
Neutral	.10*	.09	.09	.26**	.26	-1.28	.10	0 (0-.24)	.16 (0-.29)	.84 (0-.98)
Unpleasant	.24**	.35**	.35	.13	.13	**1.77**	**<.05**	.31 (.05-.44)	0 (0-.18)	.69 (.56-.84)

Note: *r*= Pearson's *r;* Z-scores are based on comparisons of ICCs for MZ and DZ twins; A^2= Heritability estimate/ additive genetic influence, C^2= shared environmental influence, E^2= nonshared environmental influence; *= $p<.05$, **=$p<.01$. Significant *Z*-score values (and accompanying *p*s) are bolded.

Table 4. Split-half reliabilities, and twin concordances for ERP residual scores (pleasant controlling for neutral, and unpleasant controlling for neutral) reflecting variance attributable to emotion processing.

ERP Variable	Split-Half	MZ concordance		DZ concordance		Comparison		ACE estimates (90% CI)		
	r	*R*	ICC	*r*	ICC	*Z*	*p*	A^2	C^2	E^2
EPN (175-275 ms) Oz										
Pleasant	.10*	.07	.07	-.02	-.02	.65	.26	.05 (0-.19)	0 (0-.15)	.95 (.79-1)
Unpleasant	.16**	.21*	.21	.12	.12	.67	.25	.24 (0-.41)	0 (0-.24)	.75 (.62-.95)
P300 (300-600 ms) Pz										
Pleasant	.31**	.26**	.26	.05	.05	1.57	.06	.23(1.13^{e-15}-36)	0 (0-.23)	.77 (.64-.91)
Unpleasant	.36**	.35**	.35	.06	.09	**2.00**	**<.05**	.29 (.02-.42)	0 (0-.21)	.71 (.58-.84)
P300 (300-600 ms) Fz										
Pleasant	.37**	.11**	.11	.07	.07	.29	.39	.10 (0-.26)	0 (0-.21)	.90 (.74-1)
Unpleasant	.25**	.33**	.33	.11	.11	**1.69**	**<.05**	.31 (.001-.44)	0 (0-.25)	.69 (.56-.83)
LPP (600-1000 ms) Pz										
Pleasant	.37**	.11	.11	.08	.08	.22	.42	.10 (0-.29)	.02 (0-.20)	.88 (.72-1)
Unpleasant	.43**	.17	.17	.16	.16	.07	.47	.07 (0-.35)	.09 (0-.27)	.83 (.65-.99)
LPP (600-1000 ms) Fz										
Pleasant	.37**	.17	.17	.20*	.20	-.22	.41	0 (0-.36)	.19 (0-.32)	.81 (.64-.96)
Unpleasant	.32**	.15	.15	.12	.12	.22	.41	.16 (0-.36)	.02 (0-.26)	.82 (.65-1)
LPP (1000-2000 ms) Pz										
Pleasant	.34**	.09	.09	.05	.05	.29	.39	.09 (0-.27)	0 (0-.20)	.91 (.73-1)
Unpleasant	.30**	.01	.01	-.09	-.10	.80	.21	0 (0-.13)	0 (0-.09)	1.0 (.87-1)
LPP (1000-2000 ms) Fz										
Pleasant	.41**	.29**	.29	.17	.17	.92	.18	.30 (0-.46)	0 (0-.30)	.69 (.54-.88)
Unpleasant	.31**	.25**	.25	-.07	-.07	**2.21**	**<.01**	.17 (.001-.34)	0 (0-.11)	.83 (.66-1)
LPP (2000-3000 ms) Pz										
Pleasant	.28**	.09	.09	.05	.05	.29	.39	.08 (0-.26)	.01 (0-.20)	.91 (.74-1)
Unpleasant	.08	.08	.08	.10	.10	.15	.44	0 (0-.26)	.08 (0-.21)	.92 (.74-1)
LPP (2000-3000 ms) Fz										
Pleasant	.35**	.19	.19	.13	.13	.46	.32	0 (0-.29)	.13 (0-.26)	.87 (.71-1)
Unpleasant	.23**	.21**	.21	-.08	-.08	**2.20**	**<.01**	.23 (.05-.39)	0 (0-.08)	.77 (.61-.94)

Note: *r*= Pearson's *r;* Z-scores are based on comparisons of ICCs for MZ and DZ twins; A^2= Heritability estimate/ additive genetic influence, C^2= shared environmental influence, E^2= nonshared environmental influence; *= p<.05, **=p<.01. Significant *Z*-score values (and accompanying *p*s) are bolded.

Table 5. Concordance scores for difference scores (pleasant minus neutral and unpleasant minus neutral) indicating heritability of affective processing

ERP Variable	Split-half	MZ concordance		DZ concordance		Comparison		ACE estimates (90% CI)		
	r	*R*	ICC	*r*	ICC	Z-score	*p*	A^2	C^2	E^2
EPN (175-275 ms) Oz										
Pleasant	-.007	.06	.06	-.02	-.02	.57	*.56*	.03 (0-.17)	.01 (0-.13)	.88 (.70-.95)
Unpleasant	.06	.18	.18	.13	.13	.37	*.71*	.01 (0-.12)	.01 (0-.14)	.67 (.55-.76)
LPP (300-600 ms) Pz										
Pleasant	.17**	.21*	.21	.06	.06	1.14	*.25*	.09 (0-.20)	.01 (0-.13)	.62 (.35-.78)
Unpleasant	.27**	.26*	.30	.06	.06	1.52	*.13*	.23 (.10-.30)	.03 (0-.09)	.49 (.38-.58)
LPP (300-600 ms) Fz										
Pleasant	.25**	.10	.10	.06	.06	.30	*.77*	.01 (0-.11)	.004 (0-.02)	.81 (.72-.85)
Unpleasant	.14**	.29**	.29	.09	.09	1.54	*.12*	.16 (.04-.26)	.01 (0-.09)	.50 (.41-.65)
LPP (600-1000 ms) Pz										
Pleasant	.16**	.10	.10	.08	.08	.15	*.88*	.002 (0-.04)	.004 (0-.03)	.81 (.75-.89)
Unpleasant	.28**	.16	.16	.13	.13	.23	*.82*	.004 (0-.06)	.01 (0-.04)	.71 (0-.83)
LPP (600-1000 ms) Fz										
Pleasant	.21**	.12	.12	.12	.12	0	*1.0*	0 (0-.02)	.01 (0-.03)	.77 (.68-.86)
Unpleasant	.21**	.10	.11	.18	.18	-.53	*.60*	.02 (0-.09)	.06 (0-.14)	.79 (.70-.83)
LPP (1000-2000 ms) Pz										
Pleasant	.17**	.10	.10	.01	.01	.63	*.53*	.03 (0-.11)	.006 (0-.08)	.81 (.78-.89)
Unpleasant	.10*	.02	.02	-.12	-.12	1.00	*.31*	.08 (0-.13)	.07 (0-.12)	.96 (.89-.99)
LPP (1000-2000 ms) Fz										
Pleasant	.20**	.25**	.25	.09	.09	1.18	*.24*	.10 (0-.19)	.005 (0-.05)	.56 (.20-.63)
Unpleasant	.23**	.22*	.22	-.09	-.09	**2.25**	***.02***	.28 (.13-.67)	.16 (.09-.19)	.61 (.34-.73)
LPP (2000-3000 ms) Pz										
Pleasant	.09*	.03	.03	.06	.06	-.22	*.83*	.004 (0-.01)	.008 (0-.02)	.94 (.80-1)
Unpleasant	-.12**	.07	.07	.007	.006	.45	*.65*	.02 (0-.11)	.004 (0-.02)	.86 (.76-.91)
LPP (2000-3000 ms) Fz										
Pleasant	-.002	.05	.05	.04	.04	.07	*.94*	.0004 (0-.002)	.001 (0-.03)	.90 (.81-.98)
Unpleasant	.05	.22*	.22	-.12	-.12	**2.47**	***.01***	.28 (.001-.83)	0 (0-.30)	.61 (.55-.73)

Note: *r*= Pearson's *r;* Z-scores are based on comparisons of ICCs for MZ and DZ twins; A^2= Heritability estimate/ additive genetic influence, C^2= shared environmental influence, E^2= nonshared environmental influence; *= $p<.05$, **=$p<.01$. Significant *Z*-score values (and accompanying *p*s) are bolded.

Table 6. Correlations between self-reported Trait Fear (TF) and Behavioral Inhibition (BI) and ERPs

	Correlations with raw scores						**Correlations with residual scores**					
	Full Sample		**Mz Twins**		**Dz Twins**		**Full Sample**		**Mz Twins**		**Dz Twins**	
Variable	**TF**	**BI**	**TF**	**BI**	**TF**	**BI**	**TF**	**BI**	**TF**	**BI**	**TF**	**BI**
EPN (175-275 ms) Oz	*R*	*R*	*r*	*r*	*r*	*R*	*r*	*r*	*R*	*r*	*r*	*r*
Pleasant	.04	.04	.04	.00	.03	.07	.10*	.03	.10	.01	.10	.05
Neutral	-.01	.03	-.01	-.01	-.01	.06						
Unpleasant	.04	.02	.04	-.02	.04	.07	.10*	-.001	.11	-.04	.10	.04
P300 (300-600 ms) Pz												
Pleasant	**.10***	-.05	**.12***	-.08	.09	-.01	.09	**-.13****	.13*	**-.17***	.03	-.09
Neutral	.06	.05	.04	.03	.09	.07						
Unpleasant	**.11***	-.02	.07	-.01	**.17***	-.03	**.11***	-.08	.06	-.03	**.18***	**-.15***
P300 (300-600 ms) Fz												
Pleasant	.05	-.03	.11	-.02	-.03	-.05	.08	-.03	.09	.02	.06	-.08
Neutral	-.01	-.02	.03	-.03	-.08	-.003						
Unpleasant	.01	.01	.05	.02	-.03	-.007	.06	.05	.03	.11	.10	-.02
LPP (600-1000 ms) Pz												
Pleasant	.05	-.06	.06	-.08	.05	-.05	.08	**-.15****	.09	**-.17***	.06	-.12
Neutral	-.01	.08	-.04	.07	.03	.09						
Unpleasant	.08	-.04	.05	-.04	.12	-.04	**.10***	**-.11***	.08	-.10	.13	-.11
LPP (600-1000 ms) Fz												
Pleasant	.08	-.08	.09	-.06	.06	-.09	**.10***	-.05	.09	-.02	.12	-.07
Neutral	-.03	-.02	-.03	-.04	-.03	-.003						
Unpleasant	.05	-.06	.05	-.08	.05	-.05	**.12***	-.08	**.12***	-.03	.11	-.13
LPP (1000-2000 ms) Pz												
Pleasant	.02	-.07	.003	-.11	.04	-.02	.02	-.13	.03	**-.17***	-.003	-.07
Neutral	.01	.05	-.06	.05	.10	.06						
Unpleasant	.03	.006	-.01	.02	.06	.00	.01	-.04	.02	-.01	.006	-.05
LPP (1000-2000 ms) Fz												
Pleasant	.03	-.09	.02	-.09	.04	-.10	.06	-.08	.03	-.07	.09	-.08
Neutral	-.04	-.03	-.03	-.04	-.05	-.03						
Unpleasant	-.004	-.07	.04	-.06	-.05	-.08	.03	-.04	.07	.004	-.01	-.08
LPP (2000-3000 ms) Pz												
Pleasant	-.06	-.02	-.05	-.03	-.07	-.005	-.08	-.04	-.05	-.06	-.12	-.02
Neutral	.03	.04	-.03	.04	.10	.04						
Unpleasant	-.01	.04	-.05	.05	.04	.04	-.04	.03	-.05	-.06	-.03	.02
LPP (2000-3000 ms) Fz												
Pleasant	-.03	-.06	-.05	-.02	-.01	-.10	-.02	-.04	-.02	-.01	-.01	-.07
Neutral	-.04	-.04	-.07	-.02	.02	-.06						
Unpleasant	-.02	-.004	-.02	-.02	-.03	.006	-.01	.02	.03	.03	-.04	.01

Note: *r*= Pearson's *r*; *= $p<.05$, **=$p<.01$. Significant correlations are bolded.

Table 7. Results of multiple regressions predicting ERP responses from Trait fear, Behavioral inhibition, and their interaction.

	P300 pleasant		P300 unpleasant		P300 pleasant residuals		P300 unpleasant residuals	
	β	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Trait fear	.09	.08	.09	.05	.07	.17	.08	.09
Behavioral inhibition	-.04	.31	-.01	.80	-.13*	.01	-.07	.14
Trait fear x Behavioral inhibition interaction	-.06	.20	-.04	.45	-.01	.88	.02	.64

Table 8. Interaction terms for TF/BI and pattern of emotional modulation

	F	*p*	ηp^2
EPN	.95	.46	.007
P300 (Pz)	2.52*	.02	.02
P300 (Fz)	1.75	.11	.01
LPP 600-1,000 ms (Pz)	3.38*	.003	.02
LPP 600-1,000 ms (Fz)	3.97*	.001	.03
LPP 1,000-2,000 ms (Pz)	2.25*	.04	.02
LPP 1,000-2,000 ms (Fz)	1.56	.16	.01
LPP 2,000-3,000 ms (Pz)	1.47	.18	.01
LPP 2,000-3,000 ms (Fz)	.70	.65	.005

Table 9. Means and standard deviations (sd) for each picture type by group (high/low BI and TF)

		Low BI, Low TF N=118	High BI, High TF N=127	High BI, Low TF N=91	Low BI, High TF N=87
P300 (Pz)	Pleasant	9.79 (5.93)	11.07 (5.61)	9.88 (5.77)	9.95 (5.01)
	Neutral	5.02 (5.19)	4.81 (4.87)	3.80 (5.25)	4.54 (4.47)
	Unpleasant	10.46 (6.12)	11.72 (6.14)	10.65 (5.66)	11.03 (5.25)
	Pleasant residuals	-.19 (.98)[a]	.19 (1.00)[a]	.10 (1.04)	-.04(.92)
	Unpleasant residuals	-.22 (1.00)[a]	.14 (1.07)[a]	.09 (.98)	.02 (.95)
LPP 600-1,000 ms (Pz)	Pleasant	7.13 (5.06)	7.79 (4.45)	7.54 (4.92)	6.96 (4.87)
	Neutral	2.55 (4.09)	1.79 (4.00)	1.36 (4.35)	1.98 (3.89)
	Unpleasant	8.94 (5.36)	10.17 (5.78)	9.75 (4.68)	9.52 (5.64)
	Pleasant residuals	-.18 (.97)[ab]	.16 (.96)[a]	.18 (.92)[b]	-.10 (1.00)
	Unpleasant residuals	-.23 (.94)[ab]	.17 (1.10)[a]	.15 (.89)[b]	-.02 (1.07)
LPP 600-1,000 ms (Fz)	Pleasant	4.34 (7.44)	6.36 (6.49)	6.26 (6.06)	6.05 (6.78)
	Neutral	.61 (5.75)	.99 (6.25)	.16 (5.93)	-.11 (6.77)
	Unpleasant	4.97 (7.54)	7.07 (6.56)	7.47 (6.43)	7.06 (7.2)
	Pleasant residuals	-.30 (1.06)[abc]	.05 (.90)[a]	.22 (1.07)[b]	.23 (.87)[c]
	Unpleasant residuals	-.24 (1.04)[bc]	.02 (.98)	.16 (.72)[b]	.15 (.92)[c]
LPP 1,000-2,000 ms (Pz)	Pleasant	3.16 (4.58)	3.36 (4.16)	3.63 (4.26)	2.89 (3.94)
	Neutral	1.13 (3.39)	.46 (3.67)	.32 (3.36)	1.10 (3.10)
	Unpleasant	4.11 (4.31)	4.33 (4.89)	4.67 (3.82)	4.27 (4.82)
	Pleasant residuals	-.11 (1.01)	.09 (.99)	.20 (1.03)	-.18 (.88)
	Unpleasant residuals	-.13 (.94)	.05 (1.09)	.18 (.85)	-.10 (1.09)

Note: Superscripts a,b, and c reflect significant between-group differences, with significance set to $p < .008$ (bonferroni corrected for 6 comparisons across each component/picture type)

Table 10. Biometric model fit results for the association between emotional modulation of the P300 and trait fear.

Model	ep	AIC
Trait fear- Unpleasant Pz P300		
Bivariate ACE	11	3603.61
AE	8	3597.62
CE	8	3597.61
E	*5*	*3591.65*
Trait fear- Unpleasant Residuals Pz P300		
Bivariate ACE	11	552.19
AE	8	546.20
CE	8	546.19
E	*5*	*540.20*
Trait fear- Pleasant Pz P300		
Bivariate ACE	11	3503.68
AE	8	3497.68
CE	8	3497.73
E	*5*	*3491.73*
Trait fear- Pleasant Residuals Pz P300		
Bivariate ACE	11	550.41
AE	8	544.50
CE	8	544.41
E	*5*	*538.73*

Note: ep= estimated parameters; AIC= Akaike's information criterion; lower AIC values indicate the model is a better fit. In each instance, the best fitting model is highlighted in grey.

Table 11. Biometric model fit results for the association between emotional modulation of the P300 and Behavioral inhibition

Model	ep	AIC
Behavioral inhibition- Unpleasant Pz P300		
Bivariate ACE	11	3637.71
AE	8	3631.71
CE	8	3631.71
E	*5*	*3625.74*
Behavioral inhibition- Unpleasant Residuals Pz P300		
Bivariate ACE	11	176.61
AE	8	170.61
CE	8	170.61
E	*5*	164.61
Behavioral inhibition- Pleasant Pz P300		
Bivariate ACE	11	3541.08
AE	8	3535.08
CE	8	3535.08
E	*5*	*3529.08*
Behavioral inhibition- Pleasant Residuals Pz P300		
Bivariate ACE	11	930.13
AE	8	924.28
CE	8	924.13
E	*5*	*918.77*

Note: ep= estimated parameters; AIC= Akaike's information criterion; lower AIC values indicate the model is a better fit. In each instance, the best fitting model is highlighted in grey.

Table 12. Pearson's correlations between early and late ERP components

	EPN (175-275 ms) Oz			(300-600 ms) Pz			(300-600 ms) Fz		
P300 (300-600 ms) Pz	P	N	U	P	N	U	P	N	U
Pleasant	.46**			-			-		
Neutral		.42**			-			-	
Unpleasant			.47**			-			-
P300 (300-600 ms) Fz									
Pleasant	.10*			.50**			-		
Neutral		.07			.51**			-	
Unpleasant			.09*			.47**			-
LPP (600-1000 ms) Pz									
Pleasant	.41**			.71**			.46**		
Neutral		.33**			.70**			.45**	
Unpleasant			.28**			.46**			.40**
LPP (600-1000 ms) Fz									
Pleasant	.14**			.47**			.84**		
Neutral		.08			.44**			.83**	
Unpleasant			.13**			.43**			.81**
LPP (1000-2000 ms) Pz									
Pleasant	.36**			.45**			.28**		
Neutral		.34**			.47**			.24**	
Unpleasant			.33**			.46**			.23**
LPP (1000-2000 ms) Fz									
Pleasant	.23**			.42**			.58**		
Neutral		.15**			.39**			.49**	
Unpleasant			.21**			.35**			.51**
LPP (2000-3000 ms) Pz									
Pleasant	.32**			.33**			.17**		
Neutral		.30**			.29**			.06	
Unpleasant			.26**			.10*			.13**
LPP (2000-3000 ms) Fz									
Pleasant	.22**			.36**			.43**		
Neutral		.12*			.24**			.27**	
Unpleasant			.20**			.27**			.36**

Note: *r*= Pearson's *r*; *= $p<.05$, **=$p<.01$. P= pleasant, N= neutral, U= unpleasant

Figure 1. Topographic maps for the time window of the EPN, depicting differences (in μV) in the sample as a whole for pleasant minus neutral (right) and unpleasant minus neutral (left) pictures. Also depicted are stimulus-locked ERP waveforms reflecting the average activity at Oz, referenced to an average of all electrodes. Stimulus onset is at time 0 and negative is plotted up; the time window of the EPN highlighted in gray.

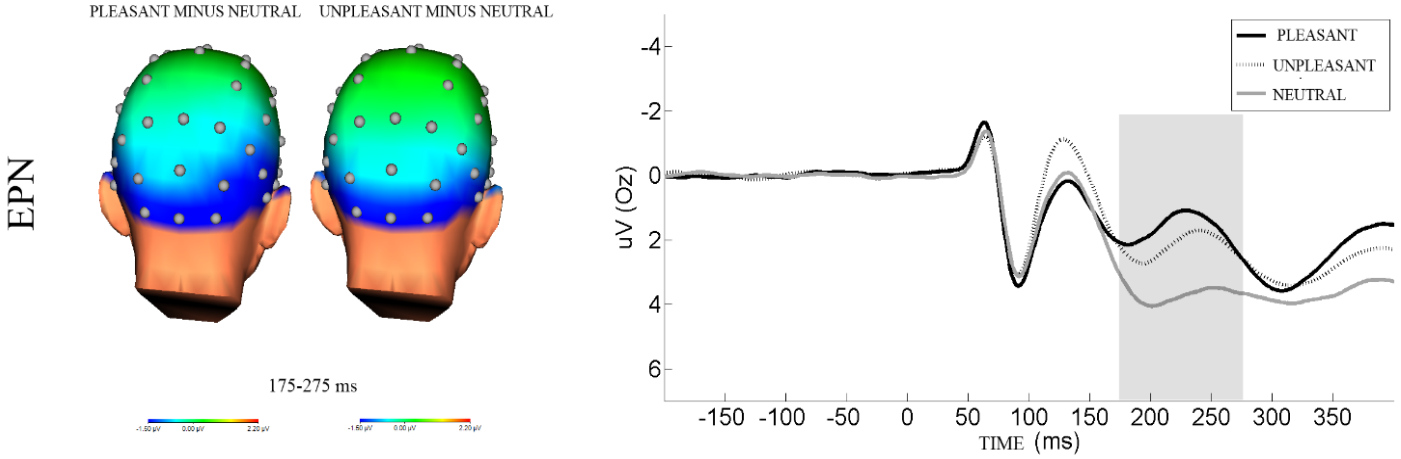


Figure 2. Topographic maps for each of the four time-windows of the LPP, depicting differences (in μV) in the sample as a whole for pleasant minus neutral and unpleasant minus neutral pictures; activity in each time-window is depicted from two angles to display parietal (left) and frontal (right) effects. Also depicted are stimulus-locked ERP waveforms reflecting the average activity at Fz (top) and Pz (bottom), referenced to an average of the mastoids. Stimulus onset is at time 0 and negative is plotted up.

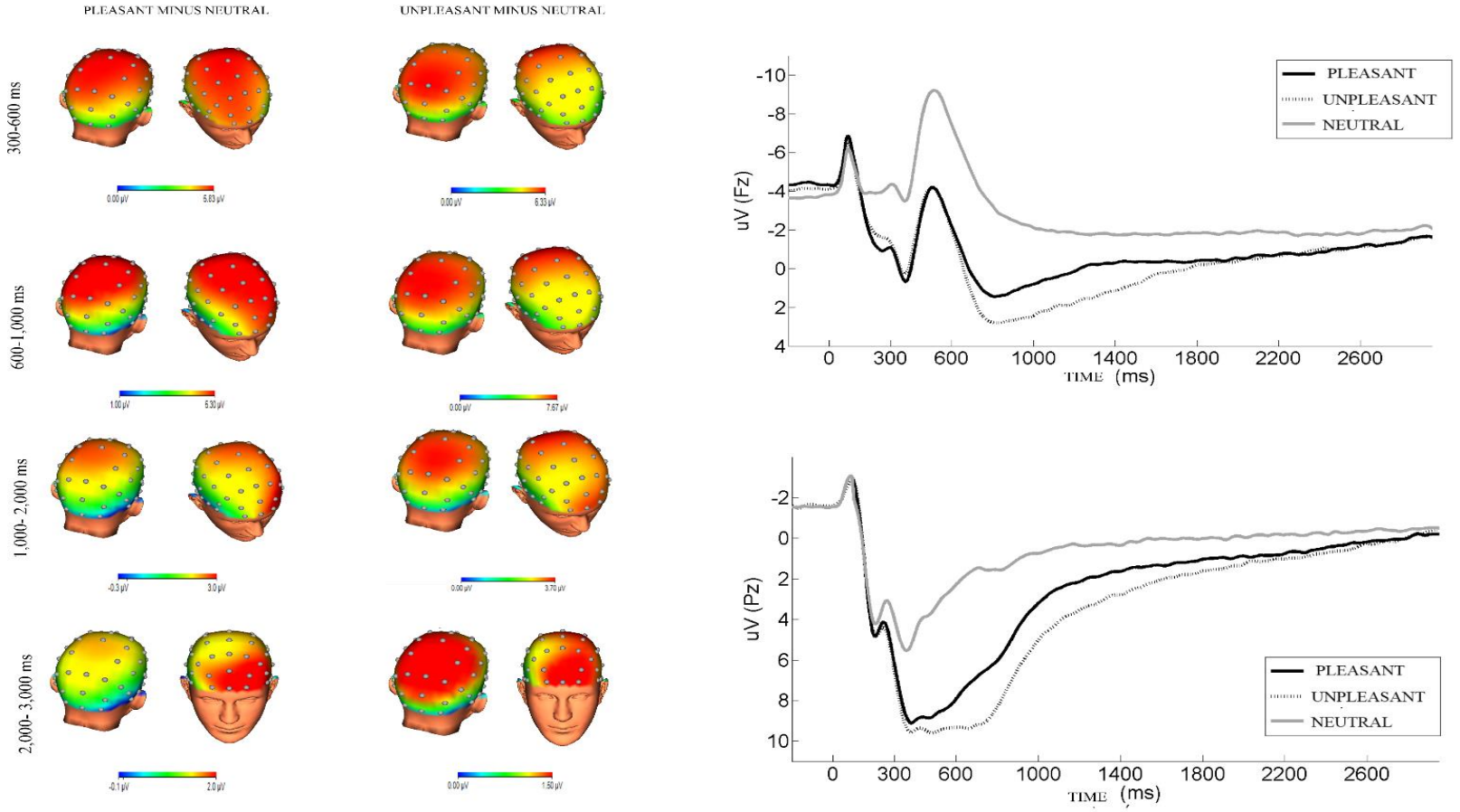


Figure 3. Stimulus-locked ERP waveforms reflecting the average activity at Fz (top) and Pz (bottom) for high and low Trait fear individuals. Stimulus onset is at time 0 and negative is plotted up.

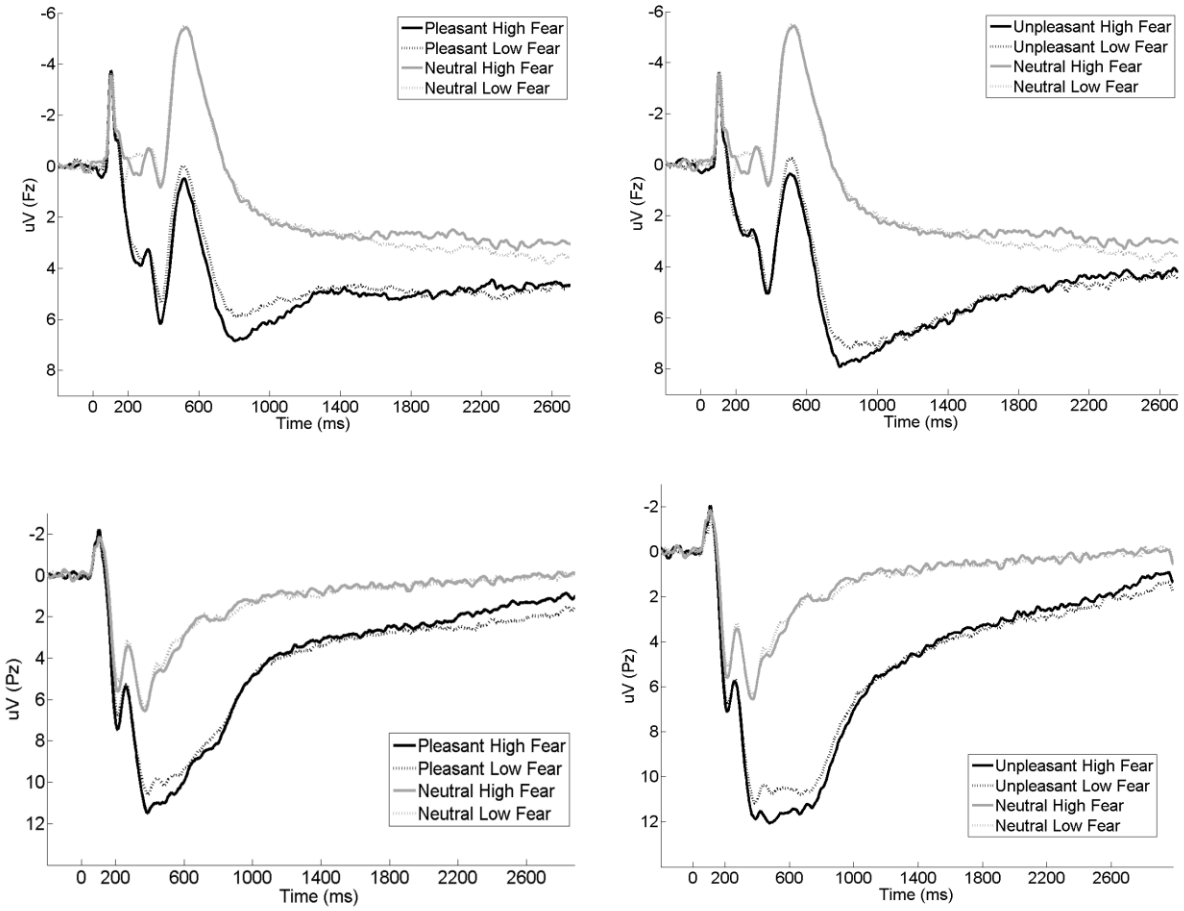


Figure 4. Stimulus-locked ERP waveforms reflecting the average activity at Fz (top) and Pz (bottom) for high and low Behavioral inhibition individuals. Stimulus onset is at time 0 and negative is plotted up.

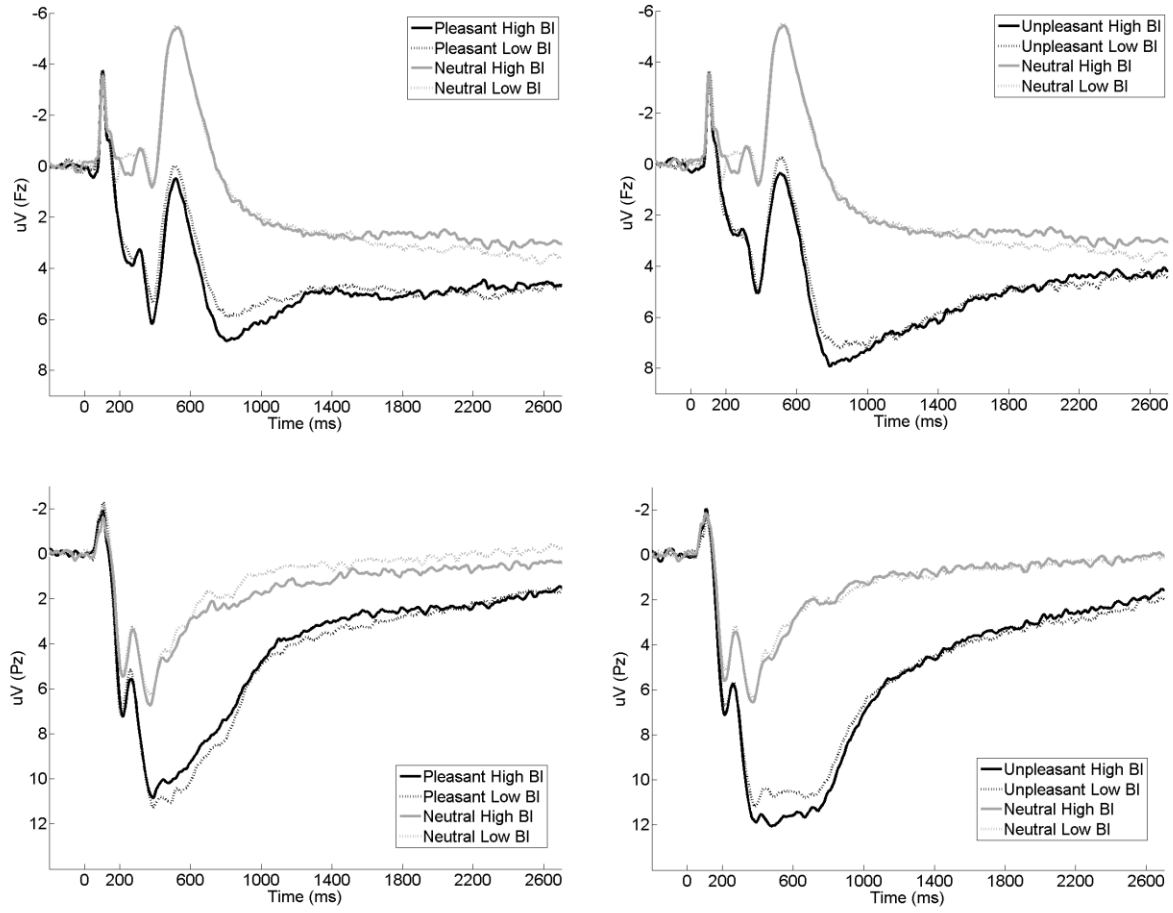
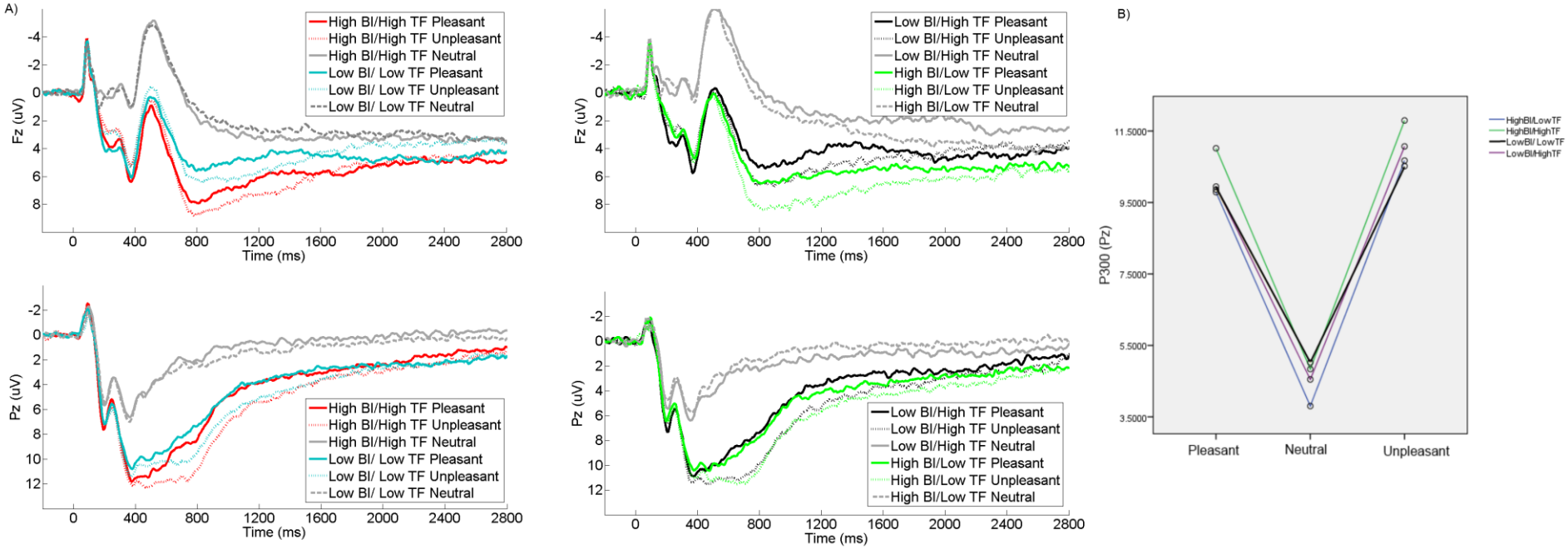


Figure 5. A) Stimulus-locked ERP waveforms reflecting the average activity at Fz (top) and Pz (bottom) for the interaction of Trait fear and Behavioral inhibition. Stimulus onset is at time 0 and negative is plotted up. B) Line graph depicting the pattern of emotional modulation for each group in the time-window of the P300 at electrode Pz.



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