Activation and Habituation of the Cingulate Cortex during Emotion Processing in Healthy Controls, Borderline, and Schizotypal Personality Disorder

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by

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Abstract

Disturbances in emotional functioning are central features of the clinical profiles of both borderline and schizotypal personality disorder (BPD and SPD, respectively). BPD is characterized by a high sensitivity to emotional stimuli and unusually strong and long-lasting reactions, indicative of impaired habituation to emotional stimuli (Linehan, 1993). Previous research suggests that SPD patients demonstrate limbic hyper-reactivity to unpleasant stimuli, at least initially, but intact habituation to repeated presentation of unpleasant stimuli (Hazlett et al., 2012). The cingulate cortex supports various aspects of emotion processing and regulation, and abnormalities of this region have been related to emotion dysfunction in SPD and BPD (Koenigsberg, Fan, et al., 2009; Modinos, Ormel, & Aleman, 2010). However, findings of functional cingulate abnormalities in the context of emotion processing have been inconsistent in BPD and limited in SPD. The current study utilized event-related functional magnetic resonance imaging (fMRI) in three groups, BPD patients, SPD patients, and healthy control individuals, during a task involving an intermixed series of unpleasant, neutral, and pleasant pictures, each presented twice within their respective trial. This approach permitted the examination of reactivity to emotional stimuli and habituation of emotional responses within the cingulate. Blood-oxygen-level dependent response values were obtained within the manually delineated anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC) and compared across groups. Compared to healthy controls and SPD patients, BPD patients exhibited significantly greater activity in the ACC during the presentation of neutral pictures. Heightened activity in the BPD group persisted across the initial and repeated presentations of neutral pictures. On the other hand, SPD patients exhibited greater activity in the ACC compared to healthy controls and BPD patients during the initial presentation of unpleasant pictures, but activity normalized when the pictures were repeated. The two patient groups demonstrated heightened ACC activation,
but these abnormalities were differentiated by associated picture-type (neutral versus unpleasant) and attenuation of the response upon repeated presentation of the stimuli. Diagnostic differences in PCC activation did not reach significance. Overall results suggest unique involvement of the ACC in BPD and SPD symptomatology.
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INTRODUCTION

Disturbances in emotional functioning are central features of the clinical profiles of both borderline and schizotypal personality disorder (BPD and SPD, respectively). BPD is characterized by a heightened sensitivity to emotional stimuli and intense reactions that are slow in returning to baseline (Linehan, 1993). These features are thought to result from a failure of “top-down” frontal processes that modulate activity in over-reactive limbic structures (Herpertz, Jeung, Mancke, & Bertsch, 2014). SPD, on the other hand, is characterized by flattened affect and anhedonia (American Psychiatric Association, 2013). Prior research suggests that SPD is associated with hyper-reactivity to aversive stimuli and normal or hypo-reactivity to positive and neutral stimuli in limbic structures (Hazlett et al., 2012; Huang et al., 2013) and increased activation of frontal, regulatory regions (Modinos, Ormel, & Aleman, 2010). The cingulate cortex is a highly heterogeneous structure and is involved in various aspects of emotion, including the modulation of mood, detection of salience of emotional stimuli, and regulation of emotional responses (Bush, Luu, & Posner, 2000). It has been found to be activated both in the initial response to emotional stimuli (Vogt, 2005) and during explicit (e.g., cognitive reappraisal) and implicit (e.g., habituation) emotion regulation (Koenigsberg et al., 2014; Ochsner, Bunge, Gross, & Gabrieli, 2002). As such, it is a region of interest in the study of disorders involving affective dysfunction. Evidence of cingulate abnormalities in BPD and SPD does exist; however, much of the existing literature on BPD is inconsistent concerning the nature of these abnormalities (e.g., see meta-analytic papers by Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2013 and Schulze, Schmahl, & Niedtfeld, 2016), and research on cingulate functioning on SPD is limited. The current study examines activity of the cingulate in three groups, BPD patients, SPD patients, and healthy control individuals, during the presentation of novel and
repeated affective pictures. This approach will allow us to examine two aspects of emotional functioning in these populations: (1) emotional reactivity and (2) habituation, an involuntary regulatory process in which an individual’s physiological or emotional reaction diminishes in response to a frequently repeated stimulus. Diagnostic specificity of the findings will be examined by including both BPD and SPD patients and comparing these two groups to healthy controls.

Background

**Borderline Personality Disorder.** BPD is characterized by a pervasive pattern of emotional instability and impaired impulse control (American Psychiatric Association, 2013). The concept of a ‘borderline personality’ was first described in 1938 by Adolph Stern, who used the label to refer to a group of patients who were believed to lie on the border between neurotic and psychotic disorders (Stern, 1938). Otto Kernberg was instrumental in establishing the modern concept of BPD, describing such patients as having a consistent pattern of functioning and behavior characterized by instability and reflecting a disturbed psychological self-organization (Kernberg, 1975). In 1975, Gunderson and Singer (1975) developed an operational definition of BPD which became the basis of the current diagnostic entity, and BPD was subsequently introduced into the DSM-III. The clinical features of BPD can be divided into three dimensions: (1) affective dysfunction including affective instability, inappropriate anger, and avoidance of abandonment; (2) behavioral dysregulation including impulsivity and suicidal or self-injurious behavior; and (3) disturbed relatedness including unstable relationships, identity disturbance, chronic feelings of emptiness, and paranoid ideation (Sanislow et al., 2002). The symptoms of BPD most often appear first in adolescence or young adulthood; however, behavioral precursors may be present earlier. These include infantile sadness, sensitivity,
frustration, and demand for attention, all greater than normal, in early childhood (Paris, 2000). While there is no cure for BPD, symptoms generally decrease with time and treatment (Gunderson et al., 2011). BPD commonly remits by early middle age (Links, Mitton, & Steiner, 1990; Paris, Brown, & Nowlis, 1987).

The point prevalence of BPD is estimated to be approximately 1.4% and lifetime prevalence around 5.9% in the general population (Lenzenweger, Lane, Loranger, & Kessler, 2007). In clinical settings, BPD is the most prevalent personality disorder, with half of patients presenting with recurrent suicide attempts meeting criteria (Grant et al., 2008). Rates of BPD are not significantly different between men and women in the general population. However, increased rates of BPD in women are found in clinical samples, perhaps due to criterion or assessment biases, increased treatment-seeking among women, sampling biases or biological or sociocultural differences (Grant et al., 2008). BPD patients utilize psychosocial treatment more frequently and in greater amounts than other disorders (Bender et al., 2001; McClure, Harvey, Bowie, Iacoviello, & Siever, 2013). BPD is also associated with significant functional impairment as individuals with BPD often have less education and are more likely to be unemployed and/or disabled compared with other psychiatric populations (Skodol et al., 2002). Impairments in social and interpersonal functioning are common as well and include distress in friendships, conflicts with friends, feelings of loneliness, and reduced social support (Hengartner, Muller, Rodgers, Rossler, & Ajdacic-Gross, 2014). Rates of suicide completion in this population have been estimated to be between 3 and 10% (McGlashan, 1986; Paris & Zweig-Frank, 2001).

**Schizotypal Personality Disorder.** First introduced in the DSM-III, SPD is characterized by a pervasive pattern of social and interpersonal deficits, restricted affect, and odd thinking and behavior. It is categorized as a schizophrenia-spectrum disorder in the DSM-5 and has a similar,
yet less severe, symptom profile to that of schizophrenia (American Psychiatric Association, 2013). The current diagnostic construct of SPD was based largely on clinical profiles of patients labeled with “borderline schizophrenia” in the landmark Danish adoption schizophrenia studies (D. Rosenthal, Wender, Kety, Welner, & Schulsinger, 1971). These patients were family members of schizophrenia patients and exhibited a syndrome resembling an attenuated form of schizophrenia. This syndrome was presumed to share a genetic substrate with chronic schizophrenia and formed the basis for the DSM-III criteria for SPD developed by Spitzer and colleagues (1979). SPD is still commonly viewed as an attenuated form of schizophrenia, sharing core deficits in cognitive and social functioning. However, patients with SPD lack the recurrent or chronic psychosis seen in schizophrenia (Siever & Davis, 2004). Family and adoptive studies show higher rates of SPD in the relatives of schizophrenia patients than other groups, supporting a genetic relationship between the two disorders (Kendler et al., 1993; Onstad, Skre, Edvardsen, Torgersen, & Kringlen, 1991). SPD and schizophrenia share a number of phenomenological, cognitive, genetic, and neuroanatomical markers (American Psychiatric Association, 2013; Dickey et al., 1999; McClure et al., 2007; Tomppo et al., 2009). As such, SPD provides a useful model for the study of schizophrenia spectrum disorders while minimizing the confounding effects of long-term use of antipsychotic medication, hospitalizations, and chronic and severe functional impairment that often plague schizophrenia research. Furthermore, studying SPD can reveal neuroprotective factors that prevent these patients from developing full-blown schizophrenia (Siever & Davis, 2004).

Illness onset usually occurs in late adolescence or early adulthood with the risk period for SPD ending around 40 years of age (Baron, Gruen, Asnis, & Kane, 1983). However, signs of the disorder may be present in childhood or younger adolescence in the form of social impairment,
unusual interests and behaviors, poor academic performance, high levels of social anxiety, and a preference for solitary activities (Esterberg, Trotman, Brasfield, Compton, & Walker, 2008). SPD has a relatively stable course, with few patients going on to develop schizophrenia or another psychotic disorder; however, symptoms may decrease modestly with age (American Psychiatric Association, 2000; Pulay et al., 2009). The lifetime prevalence of SPD in the United States is estimated to be 3.9%, with significantly greater rates in men (4.2%) than women (3.7%). Odds of SPD are significantly greater in black women, individuals with lower income, and those that are separated, divorced, or widowed; odds are significantly lower in Asian men (Pulay et al., 2009). SPD patients are reported to have more psychiatric hospitalizations and halfway house stays than those with other personality disorders and major depressive disorder and have a higher likelihood of having received antipsychotic medications than those with major depressive disorder (Bender et al., 2001). Despite having more extensive treatment histories, SPD patients continue to function at levels lower than other personality disorders following treatment (Mehlum et al., 1991). Patients with SPD are less likely to hold a bachelor’s degree or higher, to be employed, and to be living independently compared to healthy controls and other psychiatric populations (McClure et al., 2013; McGurk et al., 2013; Skodol et al., 2002). Social and interpersonal difficulties are also common. SPD is associated with distress and conflicts in friendships, feelings of loneliness, few close friends, and reduced social support (Hengartner et al., 2014).

**Emotion Impairments**

The current study examines neural correlates of emotion processing in BPD and SPD. This section includes a brief overview of current knowledge about impairments in emotion
functioning in these disorders, with special attention to affect reactivity and regulation of emotional responses.

**Borderline Personality Disorder.** Emotion dysregulation is a core clinical feature of BPD and has been postulated to be the primary source of behavioral dysfunction in this population (Linehan, 1993). It is characterized behaviorally by a high sensitivity to emotional stimuli, with reactions that are more intense and slow to return to baseline (Linehan, 1993). Theories of emotion regulation propose a balance between top-down cortical modulation and bottom-up limbic arousal in healthy individuals (Davidson, Putnam, & Larson, 2000; Ochsner & Gross, 2007; M. L. Phillips, Drevets, Rauch, & Lane, 2003). Dysregulation of emotion in BPD may result from an imbalance of these systems (Krause-Utz, Winter, Niedtfeld, & Schmahl, 2014). As described below, BPD research has largely supported the notion that affective instability results from both limbic hyper-reactivity to emotional stimuli and diminished cortical regulation of these responses.

Self-report and psychophysiological data indicate that BPD patients react more intensely to emotional stimuli. Self-reported affect reactivity is positively associated with BPD symptoms and features (Flett & Hewitt, 1995; M. Z. Rosenthal, Cheavens, Lejuez, & Lynch, 2005; Yen, Zlotnick, & Costello, 2002) and BPD patients report higher affect reactivity compared to patients with other personality disorders and bipolar II disorder (C. Henry et al., 2001; Koenigsberg et al., 2002). Psychophysiological research indicates that BPD patients exhibit increased skin conductance response, eye-blink response, and/or heart rate when presented with startling tones (Ebner-Priemer et al., 2005; Grootens et al., 2008) and when viewing unpleasant pictures (Hazlett et al., 2007) and pictures depicting self-injurious behavior (Welch, Linehan, Sylvers, Chittams, & Rizvi, 2008), as well as in everyday life (Ebner-Priemer et al., 2007).
Psychophysiological measures may be modulated by symptom severity (Bichescu-Burian, Steyer, Steinert, Grieb, & Tschoke, 2016; Limberg, Barow, Freyberger, & Hamm, 2011).

Neuroimaging research has demonstrated volumetric and functional abnormalities in various limbic structures involved in the processing of emotional stimuli (LeBoeuf, Guile, Labelle, & Luck, 2016; O'Neill et al., 2013; Schulze et al., 2016). The amygdala, a region important in detecting and processing emotionally salient events and initiating stress and fear responses (Ochsner & Gross, 2007), has been studied extensively in this population and has largely been found to have decreased volume (Niedtfeld et al., 2013; Nunes et al., 2009; Tebartz van Elst et al., 2003) and to be overactive in response to negatively-valenced emotional stimuli (Donegan et al., 2003; Hazlett et al., 2012; Herpertz et al., 2001; Schulze et al., 2016). A handful of studies have failed to find differences or have found less activation in this region (e.g., Ruocco et al., 2013), but this may be due to the confounding effects of medication status, dissociative states, and comorbidities of the patient samples (Krause-Utz et al., 2014; Schulze et al., 2016). Heightened activity in other limbic regions, including the hippocampus and insula, during the processing of aversive stimuli has also been observed in this population (Koenigsberg, Fan, et al., 2009; Niedtfeld et al., 2010; Ruocco et al., 2013; Scherpiet et al., 2014; Schulze et al., 2016).

While research has been rather consistent in demonstrating hyper-reactivity to unpleasant emotional stimuli in BPD patients, findings are still mixed in regards to reactivity to neutral and pleasant stimuli. One study found that while BPD patients reported heightened negative affect intensity and reactivity, they reported similar levels of positive affect compared to healthy controls (Levine, Marziali, & Hood, 1997). They also rate pleasant pictures as less pleasant than healthy controls (Hazlett et al., 2012; Herpertz, Kunert, Schwenger, & Sass, 1999). BPD patients demonstrate lower heart rate compared to healthy controls and patients with avoidant
personality disorder in response to positive stimuli (Herpertz et al., 2000). On the other hand, a few studies have indicated that BPD patients may be hyper-reactive to pleasant stimuli, at least on a neural level. For example, increased activation of the amygdala has been observed in BPD patients when presented with happy faces (Donegan et al., 2003), including when they were presented below the level of conscious awareness (Baskin-Sommers et al., 2015).

Research examining reactivity to neutral stimuli in BPD suggests a tendency for these patients to interpret neutral stimuli as unpleasant. BPD patients have been shown to rate neutral stimuli as less pleasant (Herpertz et al., 1999) and to interpret neutral facial expressions as negative (Mitchell, Dickens, & Picchioni, 2014). On a neural level, BPD patients have exhibited elevated activation in the amygdala during the presentation of neutral pictures (Donegan et al., 2003; Schulze et al., 2011), perhaps reflecting a tendency in these patients to perceive threat when there is none (M. Z. Rosenthal et al., 2008). On the other hand, BPD patients did not exhibit differences in startle eye blink compared to healthy controls during the presentation of neutral stimuli (Hazlett et al., 2007). Overall, BPD patients are hyper-reactive to aversive stimuli, and there is some evidence to suggest that they may also be hyper-reactive to pleasant and neutral stimuli, at least on a neural level. However, this line of research needs further examination due to inconsistencies.

BPD is also characterized by dysfunctional regulation of emotion. Emotion regulation is defined as processes that amplify, attenuate, or maintain an emotion (Fairholme & Manber, 2015). BPD patients are believed to have a deficit of affective regulation strategies (e.g., cognitive reappraisal and distancing), and a surplus of maladaptive regulation strategies (e.g., rumination and thought suppression), which serve to increase negative affect (Baer & Sauer,
Additionally, self-reported levels of affective control are inversely related to the number of BPD traits of an individual (Yen et al., 2002).

The prefrontal cortex (PFC) is important for modulating negative affective responses and regulating activity of the amygdala (Davidson et al., 2000), and dysfunction in this region could underlie emotion dysregulation in BPD. Decreased volume (P. Soloff, Nutche, Goradia, & Diwadkar, 2008), and reduced white matter connectivity in frontal regions have been found in BPD patients (Carrasco et al., 2012; Rusch et al., 2010). Furthermore, reduced functional connectivity between the amygdala and PFC has been reported in BPD patients (Baczkowski et al., 2016; New et al., 2007). BPD patients also exhibit decreased activation in frontal regions implicated in emotion regulation during the use of reappraisal and distancing (Koenigsberg, Fan, et al., 2009; Schulze et al., 2011).

Dysregulation of emotion manifests in prolonged emotion responses that are slow to return to baseline in BPD patients (Linehan, 1993). Prolonged responding has been demonstrated on a neural level by a delayed return to baseline activation of the amygdala following the presentation of emotional stimuli in BPD patients (Hazlett et al., 2012). Furthermore, attenuated habituation of the amygdala has been demonstrated in this population (Hazlett et al., 2012; Kamphausen et al., 2013). Habituation may be thought of as a form of automatic emotion regulation in which an individual’s physiological or emotional response diminishes in response to a frequently repeated stimulus (Thompson et al., 2014). Habituation of the amygdala (i.e., decrease in activation) to repeated pictures of emotional faces and pictures is a well-documented phenomenon (Breiter et al., 1996; Fischer, Furmark, Wik, & Fredrikson, 2000). However, when emotional pictures are presented, BPD patients demonstrate attenuated habituation of the amygdala; in other words, activation of the amygdala does not decrease as
pictures are repeated (Hazlett et al., 2012). Attenuated habituation of the amygdala has also been demonstrated in BPD patients during repeated anticipation of an aversive stimuli (Kamphausen et al., 2013). Furthermore, BPD patients failed to activate the dorsal ACC (dACC), a regulatory region, upon repeated presentation of aversive stimuli. Healthy controls, on the other hand, did exhibit increased activity of this region (Koenigsberg et al., 2014).

In summary, dysregulation of emotion in BPD is characterized by strong reactions that are abnormally slow in returning to baseline. Structural and functional abnormalities in limbic and frontal structures are likely a neural underpinning of impaired emotion regulatory mechanisms in BPD. The failure of inhibitory regions to modulate over-active limbic structures may result in abnormally strong and prolonged responses to emotional stimuli.

**Schizotypal Personality Disorder.** One of the core clinical features of SPD is restricted affect which includes constricted emotional experience and expression, indifference, and coldness (American Psychiatric Association, 2013). Despite the central importance of disordered affective functioning in SPD, neural models of emotion dysfunction are much less developed in SPD than BPD. Only a handful of studies have examined affect reactivity and regulation in this population and are reviewed below.

Self-report measures suggest that SPD patients demonstrate blunted reactivity to emotional stimuli. For example, SPD patients report higher levels of alexithymia, a personality construct characterized by difficulties in experiencing, identifying, and expressing emotions (Dickey et al., 2012). They also rate unpleasant pictures as less unpleasant and pleasant pictures as less pleasant (Hazlett et al., 2012). However, neuroimaging and psychophysiological data suggest intensified reactivity, at least on a neural level. One such study found that when SPD patients were presented with novel unpleasant emotional pictures, they demonstrated
significantly greater amygdala activation compared to healthy controls (Hazlett et al., 2012). Furthermore, heightened skin conductance response to aversive stimuli in childhood and greater left hemisphere EEGs during a continuous performance task are significant risk factors for the later development of SPD (Raine, Venables, Mednick, & Mellingen, 2002). Brain regions important in the processing of emotional stimuli have also been shown to be structurally abnormal in SPD, including reduced volumes of the hippocampus, amygdala, and insula (Hazlett et al., 2008; Suzuki et al., 2005; Yoneyama et al., 2003), although findings have been inconsistent (Hazlett et al., 2005; Takahashi et al., 2005). White matter tracts connecting medial temporal structures such as the amygdala and hippocampus to the frontal lobe have reduced fractional anisotropy in SPD patients (Nakamura et al., 2005).

Schizotypy refers to a collection of traits related to SPD such as odd beliefs, magical thinking and odd and eccentric behavior. Healthy individuals exhibiting these traits on a sub-clinical level are commonly thought to lie on the schizophrenia spectrum. The study of schizotypy in non-clinical populations is relevant to the study of SPD and can supplement current findings in SPD, which are limited. Individuals high on positive schizotypy demonstrate increased activity in the amygdala and hippocampus during the presentation of negative distractor words during an emotional Stroop task (Mohanty et al., 2005) and an attentional disturbance in the presence of negative, but not positive, affective stimuli (Mohanty et al., 2008). These findings further support hyper-reactivity to aversive stimuli in SPD, at least on a neural level. Hyper-reactivity may seem contradictory to restricted expression and experience of emotion associated with SPD; however, one possibility is that there is a disconnect between a patient’s subjective and physiological experience of emotion. SPD is associated with blunted subjective, self-reported experience of emotion and observable expression of emotion. However,
an individual may experience heightened physiological reactions which may not translate to observable or reportable experience. Furthermore, SPD is associated with anxiety and paranoia (American Psychiatric Association, 2013), which may contribute to heightened emotional response (Etkin & Wager, 2007; Green & Phillips, 2004). In fact, anxiety has been found to partially mediate the relationship between positive schizotypy and attentional disturbance by negative affective stimuli (Mohanty et al., 2008). Lastly, heightened emotional reactivity may also depend on the symptom profile of the individual as evidence suggests individuals high on positive symptoms may be more reactive to aversive stimuli than those with a primarily negative symptomatology (Mohanty et al., 2008).

On the other hand, a handful of findings indicate that reactivity to positive and neutral stimuli is not impaired or even diminished in SPD. Individuals high on schizotypy demonstrate lower activation of limbic regions in response to dynamic faces indicating pleasure (Huang et al., 2013) and a relative’s positive comments (Premkumar et al., 2013). Furthermore, no differences in amygdala activation were found between SPD patients and healthy controls when viewing novel positive and neutral stimuli (Hazlett et al., 2012).

In examining regulation of emotional responses, a handful of studies have hinted at an exaggerated use of emotion regulatory strategies and/or over-activity in prefrontal, regulatory regions. As described above, SPD patients demonstrated increased activation in the amygdala when unpleasant pictures were initially presented; however, when those pictures were repeated, SPD patients subsequently demonstrated lower-than-normal amygdala activation compared to healthy controls (Hazlett et al., 2012). These results indicate that SPD patients exhibit intact, and even exaggerated, habituation to emotional stimuli. Furthermore, when individuals high on positive schizotypy were asked to use the strategy of reappraisal, they reported successful
diminishment of experienced negative emotion and heightened activity of several prefrontal regions; however, they also failed to decrease activation in the amygdala and demonstrated less prefrontal-amygdala coupling (Modinos, Ormel, et al., 2010), indicating prefrontal modulation of amygdala activity may be inefficient in schizotypy. Increased activation in prefrontal regions in high positive schizotypy individuals has also been found during an affective interference task (Mohanty et al., 2005), a Theory of the Mind task (Modinos, Renken, Shamay-Tsoory, Ormel, & Aleman, 2010), and while judging personality traits about the self (Modinos, Renken, Ormel, & Aleman, 2011). Individuals high on schizotypy demonstrate difficulty in the amplification of emotion but not suppression of emotion; blunted affect, in particular, is associated with increased use of suppression (J. D. Henry et al., 2009).

Structural abnormalities of the prefrontal cortex in SPD have also been found. Increased volume of Brodmann Area 10 of the PFC has been found in SPD patients (Hazlett, et al., 2008). Also, cortical thickness of the dorsolateral PFC is positively correlated with schizotypy (Kuhn, Schubert, & Gallinat, 2012). Such findings have led some to conjecture that the PFC is preserved in SPD in contrast to schizophrenia and may represent a neuroprotective factor preventing the development of schizophrenia in individuals presumed to be at a genetic risk (Hazlett, Goldstein, et al., 2012).

In short, evidence suggests that SPD patients, similar to BPD patients, are hyper-reactive to aversive stimuli; however, they differ from BPD in that SPD patients appear to have normal or low reactivity to positive and neutral stimuli. Furthermore, regions of the frontal lobe have been found to be over-active, although it is unclear whether enhanced frontal activity translates into successful modulation of emotion. Impaired prefrontal-amygdala connectivity may mean that stronger activation in regulatory regions is needed to inhibit activation of limbic structures, or
hyper-reactivity of limbic structures may require greater recruitment of inhibitory processes. However, in terms of habituation, there does appear to be successful modulation, even to a greater degree than healthy controls, of amygdala activity in the presence of repeated aversive stimuli. Exaggerated habituation may bring SPD patients back down to a diminished baseline of emotional arousal. Further research is needed to clarify the nature of abnormalities in neural regulation of emotional responses in SPD as findings have not been consistent. Also, research on emotion processing in this population is limited and often utilizes non-clinical subjects with elevated psychometric schizotypy. These findings need to be confirmed in SPD patients.

**Cingulate Cortex**

The cingulate cortex is part of the limbic lobe and a prominent component of the medial wall of the cerebral cortex. It forms an arch running from the rostral subgenual area towards the parahippocampal gyrus, following the superior surface of the corpus callosum. As an integral part of the limbic system, the cingulate cortex has been implicated in a wide range of functions such as emotion, memory, attention, motor, and learning processes. The following review will focus on functions of the cingulate relevant to affective processing. The cingulate cortex is an important neural component of affective processing and has been shown to be activated when participants are presented with both negatively and positively-valenced stimuli (Garfinkel & Critchley, 2014; Machado & Cantilino, 2016; Phan, Wager, Taylor, & Liberzon, 2004; Vogt, 2005). It is traditionally divided into an anterior region, most commonly associated with emotion and cognitive functions, and a posterior region, often associated with memory and an important part of several intrinsic control networks (Figure 1).
Figure 1

The Cingulate Cortex

A sagittal view of the brain shows the cingulate cortex which forms an arch that follows the superior surface of the corpus callosum. The ACC is composed of the ventral ACC and dorsal ACC. The ventral ACC is further divided into the subgenual ACC (sgACC) and pregenual ACC (pgACC).
Anterior Cingulate Cortex. The ACC has been widely implicated in several aspects of affective functioning. Lesions to this region result in emotional disturbances including apathy and emotional instability (Bush et al., 2000). Researchers often further the divide the ACC further into a ventral “affective” division and dorsal “cognitive” division based on function and cytoarchitecture (Bush et al., 2000). There is evidence of reciprocal suppression of the affective division during cognitive tasks and vice versa (Bush et al., 2000), although more recent findings indicate that the cognitive division is also an important component of emotion processing (Etkin, Egner, & Kalisch, 2011).

The affective subdivision of the ACC is highly interconnected with limbic and paralimbic structures including the amygdala, orbitofrontal cortex, periaqueductal gray, and nucleus accumbens and is involved in the assessment of the salience of emotional information and the regulation of emotional responses (Bush et al., 2000). The subgenual portion of the vACC (sgACC) regulates visceral and autonomic responses to emotionally salient stimuli and shows increased activity during tasks involving sadness induction (Phan et al., 2002). It has also been implicated in extinction learning to previously fear-conditioned stimuli (Phelps, Delgado, Nearing, & LeDoux, 2004). The pregenual region (pgACC) responds to more diverse types of emotionally valenced or autonomically arousing stimuli (Bush et al., 2000; Critchley et al., 2003), particularly stimuli denoting happiness (Vogt, 2005). The vACC is thought to inhibit negative processing in the amygdala, a function that may be recruited by higher-order brain regions such as the prefrontal cortex and the dorsal division of the ACC (Etkin et al., 2011). As such, it may serve as a mediator between these higher-order regions and the amygdala (Etkin et al., 2011). Furthermore, this region has been implicated in a negative feedback loop with the amygdala which links amygdala to sgACC to supragenual ACC (BA 32) and back to the
amygdala (Pezawas et al., 2005; Stein et al., 2007). The amygdala is thought to provide bottom-up emotional information to the sgACC. In turn, amygdala activation is inhibited by the supragenual region of the ACC (Stein et al., 2007).

The dACC is considered the “cognitive” division of the ACC and is implicated in a variety of functions such as error detection/performance monitoring, modulation of attention, cognitive control, motor planning, and reward assessment (Botvinick, Cohen, & Carter, 2004; Bush et al., 2002). It has extensive connections with prefrontal and parietal cortices as well as the motor system and frontal eye fields (Vogt, 2009). Despite its characterization as a primarily cognitive region, the dACC also appears to play a significant role in emotion regulation. Activity in the dACC has been associated with reappraisal of emotional stimuli (Ochsner et al., 2002; Phan et al., 2005) and suppression of negative thoughts (Gillath, Bunge, Shaver, Wendelken, & Mikulincer, 2005) and is thought to mediate the expression of conditioned fear (Milad et al., 2007). It is also implicated in attentional control in the presence of emotional distractors (Luo et al., 2007) and the appraisal and expression of fear and anxiety (Etkin et al., 2011). As noted above, the dACC may regulate activity in the amygdala (Stein et al., 2007), potentially via the vACC (Etkin et al., 2011). While the dACC is active during emotion regulation and tasks with cognitive components, it is mostly inactive during exposure to simple emotional stimuli (Phan et al., 2002); however, there is evidence of activity in response to fearful stimuli in the most anterior part of the dACC (Vogt, 2005) as well as involvement in the emotional aspect of pain (Rainville, Duncan, Price, Carrier, & Bushnell, 1997).

Posterior Cingulate Cortex. The PCC is located within the medial portion of the inferior parietal lobule and is vastly anatomically connected with a high baseline metabolic rate (Hagmann et al., 2008; Raichle et al., 2001). It is part of the default mode network, a specific set
of brain regions which are activated when an individual is engaged in internal tasks and not focused on the outside world (Buckner, Andrews-Hanna, & Schacter, 2008). The PCC demonstrates increased activity when an individual retrieves autobiographical memories, plans for the future, or during freethinking (Addis, Wong, & Schacter, 2007; Gusnard, Akbudak, Shulman, & Raichle, 2001). This region may play an important role in internally directed cognition and controlling the balance between internally and externally focused thought (Raichle et al., 2001) as well as memory functions (Gainotti, Marra, Villa, Parlato, & Chiarotti, 1998).

While the ACC is generally thought of the emotional portion of the cingulate, the PCC may also be important in emotion processing. When exposed to positively- and negatively-valenced emotional stimuli, the PCC is activated (Vogt, 2005). Greater activation of the PCC during the evaluation of threat-related words compared to neutral words has been reported (Maddock & Buonocore, 1997). Abnormal patterns of PCC activity have been observed in various emotional disorders (Andreasen et al., 1997; Haznedar et al., 2004; Ho et al., 1996) and correlate with anxiety symptoms (Bench et al., 1992; McGuire et al., 1994; Perani et al., 1995; Reiman et al., 1997). The functions of the PCC may extend beyond internally directed cognitive processes; it potentially serves as a mediator between emotion and memory-related processes by assessing of self-relevance of emotional events and stimuli, potentially via reciprocal connections with the sgACC (Maddock et al., 2003; Vogt, 2005).

To summarize, the cingulate cortex is a highly heterogeneous structure which supports numerous cognitive and emotional functions. In terms of emotion, research indicates that the sgACC and pgACC are involved in the modulation of autonomic response, evaluating the salience of emotional information, and modulating amygdala activity. The dACC is a primarily cognitive and regulatory region; it is thought to be part of a network which can regulate
emotional responses and recruit inhibition of the amygdala via the vACC. The PCC is activated during the presentation of emotional stimuli and may work in concert with the ACC, via reciprocal connections with the sgACC, to evaluate the self-relevance of emotional stimuli.

**Habituation and the Cingulate**

Habituation is the decrement of response to repeatedly presented stimuli and, in the context of emotion processing, may be thought of as a form of automatic emotion regulation. Habituation on the neural level is critical in limiting the utilization of attentional resources for stimuli that are no longer salient (Siddle, 1991). Activity of structures such as the amygdala and hippocampus is known to decrease in healthy subjects when repeated emotional pictures are presented (Breiter et al., 1996; Fischer et al., 2000). Other brain regions, such as the dorsolateral prefrontal cortex and dACC, demonstrate increases in activity with exposure to repeated emotional stimuli (Denny et al., 2014; Koenigsberg et al., 2014), suggesting these areas may be responsible for regulatory processes that modulate habituation in other regions. However, these findings have been inconsistent (Wright et al., 2001).

The unusually strong and long-lasting reactions to emotional stimuli observed in BPD suggest that neural habituation is impaired. As previously described, BPD patients exhibit attenuated habituation of the amygdala. On the other hand, SPD patients demonstrate effective amygdala habituation to unpleasant stimuli. Therefore, divergent patterns of habituation may be one way to distinguish these disorders.

The role of the cingulate cortex in emotion, attentional, and memory processes suggest that it is a region relevant to the process of habituation of affect. Previous research has reported a decrease in activation of the pgACC upon repeated exposure to aversive stimuli (Phan, Liberzon, Welsh, Britton, & Taylor, 2003). The authors interpreted the decrease as a diminished
need for the evaluation of salience and internal generation of emotion, both processes associated 
with this region. Additionally, as the amygdala habituates, there is less demand for inhibitory 
control either directly by the pgACC or from other cortical areas via the pgACC (Phan et al., 
2003). On the other hand, activity in the dACC and PCC has been reported to increase upon 
repeated exposure to emotional stimuli (Denny et al., 2014; Koengisberg et al., 2014). The 
dACC is thought to be an important neural component of cognitive reappraisal of emotional 
content and, more generally, voluntary regulation of emotion and cognitive control. As such, the 
increase in activation of the dACC may reflect regulatory or cognitive processes that are part of 
the habituation of affect. On the other hand, an increase in activation of the PCC upon the 
presentation of repeated stimuli is likely to reflect memory retrieval processes (Denny et al., 
2013).

Cingulate findings in BPD and SPD

As previously discussed, BPD and SPD have been associated with both abnormal affect 
reactivity and emotion regulation. The cingulate cortex plays an important role in both these 
aspects of emotion and, as such, is an important region in the study of the neural underpinnings 
of these disorders. The following is a review of findings of cingulate abnormalities, especially in 
the context of emotion processing and regulation, in these disorders.

Borderline Personality Disorder. Morphological investigations have reported reduced 
volume of the ACC in adult (Tebartz van Elst et al., 2003) and adolescent patients (Whittle et al., 
2009) although other researchers have failed to find volumetric differences (O'Neil et al., 2013). 
Hazlett et al (2005) examined gray and white matter separately in the cingulate gyrus found 
reduced gray matter volume in the ACC and dorsal region of the PCC. Studies utilizing voxel-
based morphometry (VBM), an imaging analysis technique that utilizes statistical probability
mapping (SPM) to investigate focal differences in brain anatomy, have also revealed reduced gray matter of the cingulate in BPD patients (Jin et al., 2016; Minzenberg, Fan, New, Tang, & Siever, 2008; P. H. Soloff et al., 2012), although use of this technique has also been inconsistent (Kuhlmann, Bertsch, Schmidinger, Thomann, & Herpertz, 2013; Rusch et al., 2003) possibly due to the high morphometric variability of the ACC which makes VBM more difficult and susceptible to errors (Whittle et al., 2009). Smaller ACC volumes may be related to BPD symptomatology such as impulsivity (Hazlett et al., 2005) as well as fear of abandonment, suicide attempts, and BPD symptom severity, at least early in the course of the illness (Goodman et al., 2011; Whittle et al., 2009). Smaller PCC volumes have also been associated with higher levels of impulsivity and irritability/assaultiveness in BPD patients (Hazlett et al., 2005). Reduced connectivity and fractional anisotropy have been observed in interhemispheric fibers connecting dorsal regions of the left and right ACC (Carrasco et al., 2012; Rusch et al., 2003).

Functional neuroimaging techniques have provided further evidence of cingulate alterations in BPD. BPD patients demonstrate greater activity in the pgACC while viewing negatively-valenced pictures compared to healthy controls (Niedtfeld et al., 2010) and higher functional connectivity between the pgACC and amygdala during the presentation of fearful faces compared to healthy controls (Cullen et al., 2011). Additionally, in anticipation of emotional stimuli, BPD patients demonstrate greater activity in the pgACC, along with the amygdala, compared to healthy controls (Scherpient et al., 2014). These results are consistent with hyper-reactivity to emotional stimuli in BPD patients in a region associated with assessing the salience of emotional stimuli. On the other hand, in a gender discrimination task of facial expressions, while BPD patients demonstrated greater activity in the pgACC when presented with angry faces, they demonstrated lower activity in both the pgACC and sgACC for fear faces.
compared to healthy controls (Minzenberg, Fan, New, Tang, & Siever, 2007). During an emotional go/no-go task, BPD patients demonstrated abnormal patterns of activation, with increased activation for the negative go and neutral go trials and decreased activation for the negative and neutral no-go trials (Silbersweig et al., 2007). Of two recent meta-analyses of fMRI studies of emotion, only one found differences in the sgACC, reporting reduced activation in BPD patients for negative vs. neutral stimuli; neither found differences in the pgACC (Ruocco et al., 2013; Schulze et al., 2016). Therefore, while some evidence does suggest a hyper-reactive vACC in BPD patients in response to emotional stimuli, there have been some inconsistent results or lack of findings in this region. Task variability may be one source of these inconsistencies. For example, the study by Minzenberg et al. (2007) required BPD patients to identify the gender of emotional faces, a task which has a strong cognitive component. Cognitive processing is thought to increase activity in more dorsal regions of the ACC while decreasing activity in the ventral regions (Bush et al., 2000), an effect which may have confounded results. Another consideration is that while the vACC is involved in the detection of emotional salience and mediation of autonomic responses (Vogt, 2009), it may also be an important region for regulating amygdala activity (Etkin et al., 2011). Therefore, decreased activation of this region could be interpreted as an impaired recruitment of inhibitory activity in this population. Furthermore, medication status and levels of dissociation of the samples are both thought to affect activation of limbic regions and may contribute to inconsistency in findings (Krause-Utz et al., 2014; Schulze et al., 2016).

The dACC is an important region for emotion regulation and is thought to inhibit activity in the amygdala. Findings of diminished activity in this region in BPD have been fairly consistent. BPD patients have demonstrated decreased activation in the dACC in anticipation of
emotional stimuli (Scherpier et al., 2014), during the presentation of traumatic memories (Schmahl, Vermetten, Elzinga, & Bremner, 2004), and during the use of the emotion regulation strategy of distancing (Koenigsberg, Fan, et al., 2009). They also fail to increase activation in this region when emotional pictures are repeated (Koenigsberg et al., 2014). One meta-analysis found decreased activity of the dACC in BPD patients in response to negative versus neutral stimuli within a variety of tasks (Ruocco et al., 2013), while another meta-analysis failed to find any differences (Schulze et al., 2016). BPD patients comorbid with major depressive disorder also demonstrated decreased baseline activity of the dACC, a difference which was abolished following the administration of fenfluramine, a drug which causes the release of serotonin (Oquendo et al., 2005). Trait impulsivity is positively correlated with activity in the dACC in BPD patients during an affective go/no-go task, while the opposite is seen in healthy controls. Hyper-activation of this region could be compensation for elevated impulsivity (P. H. Soloff et al., 2016). Decreased functional connectivity between the dACC and the amygdala also has been exhibited in BPD patients (Cullen et al., 2011). Taken together, these findings indicate that within the context of emotion regulation, activity in the dACC is decreased in BPD patients. Diminished activity and decreased connectivity with the amygdala may hamper the regulatory functions of the dACC.

Increased activation of the PCC has been consistently found in BPD when viewing negative and, to a lesser extent, neutral pictures (Koenigsberg, Siever, et al., 2009; Niedtfeld et al., 2010) and in anticipation of emotional stimuli (Scherpier et al., 2014). Both recent meta-analyses found similar results, with increased activation of the PCC for negative vs. neutral stimuli in BPD patients (Ruocco et al., 2013; Schulze et al., 2016). Increased activation in this
region in response to emotional stimuli may reflect a tendency of BPD patients to find emotional stimuli more personally relevant.

**Schizotypal Personality Disorder.** Only a handful of studies have examined cingulate abnormalities in SPD. Volumetric investigations of this region have produced mixed results. One study found that ACC volumes in SPD patients were diminished and intermediary between schizophrenia patients and healthy controls (Takahashi et al., 2002). Two studies failed to find differences in cingulate volume between SPD patients and healthy controls (Goldstein et al., 2009; Haznedar et al., 2004). However, another study which utilized a much larger sample size found significantly smaller gray and larger white matter volumes of the cingulate in SPD patients compared to healthy controls (Hazlett et al., 2008).

A small number of fMRI studies have revealed abnormal activity of the ACC in psychometric schizotypy. One such study found that individuals high on positive schizotypy demonstrated increased activation of the dACC, among other prefrontal regions, when asked to reappraise negative content so that it no longer elicited a negative response (Modinos, Ormel, et al., 2010), suggesting an over-activity of regulatory regions in emotion processing in SPD patients. High schizotypy individuals demonstrate increased activation of the pgACC in response to dynamic faces exhibiting disappointment and decreased activation to those expressing happiness (Huang et al., 2013). High schizotypy individuals also demonstrate deactivation of the dACC during scenes of social rejection whereas those low on schizotypy demonstrate activation of the dACC, a pattern previously observed in healthy individuals. Schizotypy and SPD are associated with elevated levels of rejection sensitivity. As such, deactivation of the dACC during social rejection may reflect a downregulation of response to rejection cues in order to distance oneself from rejection scenes (Premkumar et al., 2012).
Overall, the research on functional abnormalities in the cingulate cortex in SPD is limited but some schizotypy findings suggest that it is an area of interest in this population. Findings point to heightened activity in the vACC to aversive stimuli and diminished activity to pleasant as well as increased activation of the dACC in the context of emotion regulation. These findings are in line with characterizations of SPD hyper-reactivity to aversive stimuli and hypo-reactivity to pleasant stimuli. However, further research is needed to test these results in SPD populations and expand findings by examining the cingulate in its entirety, specifically in the context of emotion processing.

**Summary**

BPD is characterized behaviorally by emotion dysregulation, specifically hyper-reactivity to emotional stimuli and strong responses that are slow to return to baseline (Linehan et al, 1993). Hyper-reactivity and attenuated habituation of limbic structures are likely to underlie emotion dysregulation in this population. Evidence indicates that BPD patients exhibit hyper-reactivity to emotional stimuli in the cingulate, particularly the vACC and PCC; however, there have been some inconsistencies in terms of findings, perhaps due to differences in tasks used during scanning and/or medication status of the patients. Activity of the dACC appears to be diminished in BPD patients in the context of emotion regulation. BPD patients exhibit attenuated habituation of the amygdala and a failure to engage the dACC during the presentation of repeated emotional stimuli. Other regions of the cingulate (i.e., vACC and PCC) have not been examined in the context of habituation to repeated emotional stimuli but may potentially contribute to prolonged emotional responding in this population and warrant further investigation. Also, cingulate abnormalities in BPD have been largely studied in the context of unpleasant stimuli even though some research suggests that hyper-reactivity in BPD may not be
limited to unpleasant stimuli only. Cingulate functioning during processing of pleasant and neutral stimuli should be further examined.

On the other hand, findings of cingulate abnormalities in SPD have been limited but do indicate that this region may be a neural substrate of emotion dysfunction in this population. Research examining psychometric schizotypy suggest that SPD may be associated with limbic hyper-reactivity to unpleasant stimuli and hypo-reactivity to pleasant stimuli. However, these findings were discovered in individuals high on psychometric schizotypy, and it is unclear whether they apply to an SPD patient population. Research on habituation is even more scarce, with only one study to date which demonstrated intact, and even exaggerated, habituation of the amgydala. Further research is needed to examine reactivity and habituation in the cingulate in this population, and how it may differentiate this disorder from BPD. The current study aims to address some of the unanswered questions concerning reactivity and habituation of the cingulate in BPD and SPD.

The Current Study

Activity of the cingulate cortex in BPD and SPD patients and healthy controls in response to novel and repeated emotional pictures will be examined. This approach will allow the examination of two aspects of emotional functioning thought to be dysfunctional in these populations: (1) reactivity to emotional stimuli, and (2) habituation to repeated emotional stimuli. The cingulate cortex has been found to be active both in the initial response to emotional stimuli and subsequent regulation of emotional responses and is thus a potential neural substrate of emotion dysfunction in these patient populations. This study aims to expand findings of functional abnormalities in the cingulate cortex in these disorders in the context of affective processing and regulation and to help clarify the nature of these abnormalities as current research
contains inconsistent findings. This is the first study to examine affect reactivity and habituation in the cingulate cortex in its entirety (i.e., both anterior and posterior regions) in BPD and SPD using the gold-standard of manually tracing the cingulate on individual MR images. This approach is more precise and potentially more powerful than whole-brain statistical mapping, the predominant methodology for analyzing fMRI data. The current study may help expand cingulate research in SPD, which is limited, and help clarify the nature of abnormalities of cingulate in BPD, as findings have been inconsistent.

Personality disorders are pervasive in the general population, often co-occur with other major mental disorders and are associated with serious functional impairment (Bender et al., 2001; Pulay et al., 2009). Furthermore, affective dysfunction is a significant risk factor for suicide (Yen et al., 2009). Therefore, emotion research in personality disorders is an important focus of study. This study aims to further understand the neural basis of alterations in emotional functioning in both BPD and SPD which can potentially help clarify our understanding of the origin and neural mechanisms of these disorders and inform better diagnostic and treatment approaches. This approach is in line with a recent movement in the research community emphasizing the need to apply basic and clinical neuroscience research findings to identify neural biomarkers in psychiatric disorders in an effort to diagnose these disorders earlier and more accurately (Casey et al., 2013; L. K. Phillips & Seidman, 2008).

This is the first study to directly compare activation of the cingulate cortex in response to emotional stimuli in BPD and SPD patients and healthy controls. While the emotional profiles of these disorders are dissimilar (i.e., BPD is characterized by emotion dysregulation and impulsivity whereas SPD is characterized by blunted affect and asocial tendencies), some biological and clinical commonalities exist among these disorders. For example, cognitive and
perceptual symptoms, such as delusions, paranoid ideation, and dissociative episodes, are common to both groups and may contribute to social impairments (Kavoussi & Siever 1992; McGlashan 1987). Excessive social anxiety and odd behaviors and beliefs are characteristic of both disorders. Furthermore, both disorders have been associated with structural and functional alterations in frontal and temporal regions. Early conceptions of “borderline schizophrenia,” which evolved into the modern concept of SPD, included symptoms related to conceptions of BPD (Spitzer, Endicott & Gibbon 1979). Comorbidity of these disorders is still relatively common, perhaps due to overlapping areas of neurocognitive abnormalities (McGlashan et al., 2000). Furthermore, many biological findings appear to be present across all personality disorders and may represent a general biological vulnerability to personality disorders (Kendler et al., 2008). As such, it is important to study these disorders together to determine diagnostic specificity of potential findings. Given the different emotional profiles of these disorders and the importance of the cingulate cortex in various aspects of emotion processing, the cingulate cortex may be one area that can distinguish these two disorders.

A further strength of the current study is the utilization of pleasant, unpleasant, and neutral emotional stimuli. Much of the research on affect reactivity and neural habituation to emotional stimuli in the cingulate is primarily focused on negative versus neutral stimuli (e.g., Denny et al., 2013; Koenigsberg et al., 2014; Phan et al., 2003), perhaps because negative emotion processing is of particular interest in many psychiatric disorders in which negative affectivity is a central feature. These include mood and anxiety disorders and some personality disorders. The current study will expand upon these findings by examining processing and habituation to unpleasant, neutral, and pleasant stimuli, to be more comprehensive. Pleasant and
unpleasant pictures are matched on arousal to eliminate the confounding effects of arousal on cingulate activity.

**Aims and Hypotheses**

The specific aims of the current study are as follows:

**Aim 1:** To examine diagnostic group differences in the activation of the cingulate during the presentation of pleasant, unpleasant, and neutral emotional pictures. Hyper-reactivity to emotional stimuli is a core feature in the emotional profile of BPD; however, it is unclear whether this hyper-reactivity is limited to unpleasant stimuli or is present during the presentation of all emotional stimuli, as has been suggested by a small number of studies (e.g., Donegan et al., 2003; Schulze et al., 2011). Findings to date suggest that SPD patients also demonstrate hyper-reactivity to unpleasant stimuli but no difference or even a lower-than-normal reaction to pleasant and neutral stimuli (Hazlett et al., 2012; Huang et al., 2013). The current study examines activation in the ACC and PCC, core components of the neural processing of emotion known to be activated in the presence of both negatively- and positively-valenced stimuli, in BPD and SPD patients and healthy controls during the presentation of unpleasant, pleasant, and neutral pictures. It is hypothesized that:

1. BPD patients will demonstrate increased activation in the ACC and PCC compared to healthy controls during presentation of all types of pictures. It is predicted that the largest effect will be observed in the unpleasant condition but that the patients will also demonstrate greater activity for pleasant and neutral pictures. These predictions are based on evidence that BPD patients demonstrate greater-than-normal activation in limbic regions in the presence of unpleasant stimuli (Hazlett et al., 2012; Niedtfeld et al., 2010) and, to a lesser extent, pleasant stimuli (Donegan et al., 2003). Evidence also points to a tendency in BPD
patients to interpret neutral stimuli as unpleasant (Mitchell et al., 2014). Therefore, it is predicted that they will also demonstrate a greater-than-normal reaction to neutral stimuli as well.

2. SPD patients will demonstrate increased activation in the ACC and PCC compared to healthy controls in the unpleasant condition only and will demonstrate no difference or even decreased activation in the pleasant and neutral conditions. This is based on evidence of greater-than-normal psychophysiological measures and neural activity in the presence of negative stimuli (Hazlett et al., 2012; Raine et al., 2002) and a lower-than-normal activity in limbic regions during the presentation of pleasant stimuli (Huang et al., 2013). Comparing the patient groups, it is predicted that the BPD and SPD groups will differ from each other in activation to the neutral and pleasant picture conditions.

**Aim 2: To examine the location of diagnostic group differences in activation within sub-regions of the ACC.** Different types of emotion are found to be processed in particular sub-regions of the ACC (i.e., the sgACC, pgACC, and, dACC). Prior research has found that the sgACC responds preferentially to sad emotional stimuli and pgACC to happy stimuli (Vogt, 2005). The dACC is a region most closely associated with cognitive functioning and regulatory aspects of emotion functioning rather than responding to simple emotional stimuli; however, the most anterior region of the dACC closest to the pgACC has been found to respond to the presentation of fearful stimuli (Vogt, 2005). Functional and/or structural abnormalities of the ACC sub-regions have been reported in BPD; however, findings have been inconsistent (e.g., Minzenberg et al., 2007; Niedtfeld et al., 2010). In SPD, limited evidence points to localized abnormalities of cingulate functioning in schizotypy (e.g., Modinos, Ormel, et al., 2010), but further study is needed to expand and confirm these findings in SPD. The current study aims to
clarify and expand current knowledge of dysfunctional ACC sub-region activity in response to emotional stimuli in these disorders. It is hypothesized that:

1. In the pleasant condition, BPD patients will demonstrate increased activation in regions known to respond to positively-valenced stimuli (i.e., the pgACC) compared to healthy controls and SPD patients. This prediction is based on evidence that BPD patients may be hyper-reactive to positively-valenced stimuli (Donegan et al., 2003) and that this sub-region of the cingulate is activated during the presentation of pleasant stimuli (Vogt, 2005). It is predicted that SPD patients will demonstrate decreased activation of the pgACC as prior evidence has demonstrated lower activity in this region during the presentation of positively-valenced stimuli in schizotypy (Huang et al., 2013).

2. In the unpleasant condition, BPD and SPD patients will demonstrate increased activation in regions known to respond to negatively-valenced stimuli (i.e., the sgACC, dACC) compared to healthy controls based on evidence that both these disorders demonstrate increased activation in response to negatively-valenced stimuli (Hazlett et al., 2012).

3. In the neutral condition, BPD patients will demonstrate increased activation in the sgACC, and the dACC. Patterns similar to those in the unpleasant condition, albeit to a lesser extent, are expected in BPD patients in the neural condition based on evidence that these patients tend to interpret neutral stimuli as negative (Mitchell et al., 2014).

**Aim 3:** To examine diagnostic group differences in change of activation of the ACC (and sub-regions) and the PCC between novel and repeated presentation of emotional pictures.

Habituation is an intrinsic emotion regulatory process in which an individual’s physiological or emotional reaction diminishes in response to a frequently repeated stimulus. The pgACC has been shown to habituate (i.e., decrease in activity) to repeated emotional stimuli in healthy
controls (Phan et al., 2003). Conversely, previous research has shown that dACC and PCC increase in activity when emotional stimuli are repeated, presumably reflecting regulatory and/or memory processes necessary for habituation in other regions (Denny et al., 2013; Koenigsberg et al., 2014). On a behavioral level, BPD is characterized by intense emotional responses that are slow to returning to baseline (Linehan, 1993), suggesting dysfunctional neural habituation of limbic structures and a failure of top-down inhibitory processes. On the other hand, SPD patients demonstrate successful habituation to unpleasant stimuli (Hazlett et al., 2012). Therefore, habituation may be an area which can distinguish these two disorders from each other.

The present study expands current knowledge of abnormalities in habituation in these disorders by examining change in activation of the cingulate during the repeated presentation of emotional stimuli. Because activity in different regions of the cingulate cortex has been shown to move in opposite directions upon repeated exposure to emotional stimuli, it is important to examine activity in each of the ACC sub-divisions. It is hypothesized that:

1. Healthy controls will demonstrate habituation (i.e., decrease in activity when pictures are repeated) for the pleasant, unpleasant, and neutral picture-type conditions in the sgACC and pgACC, the latter of which has previously been shown to habituate to emotional stimuli (Phan et al., 2003). It is also expected that activity will increase for all picture-type conditions in the dACC, a region implicated in emotion regulation, and the PCC, a region important for memory processing and self-referential thinking. Both of these regions have been demonstrated previously to increase in activation when exposed to repeated emotional stimuli (Denny et al., 2013; Koenigsberg et al., 2014).

2. BPD patients will fail to demonstrate habituation in all picture-type conditions in the sgACC and pgACC, regions implicated in the initial processing of emotional stimuli, based on
evidence of attenuated habituation of other limbic regions in this population (Hazlett et al., 2012). A failure to recruit the regulatory region, dACC, when exposed to repeated emotional stimuli is also expected, as has been demonstrated previously in this population (Koenigsberg et al., 2014). Lastly, it is expected that activity in the PCC will show a greater-than-normal increase in activity. This region has been shown to be overactive in this population (Schulze et al., 2016), likely reflecting the tendency of these patients to find emotional stimuli more personally relevant. This tendency is expected to trigger more memory and self-referential thinking processes compared to healthy controls and SPD patients.

3. SPD patients will demonstrate habituation in the sgACC and pgACC in the unpleasant condition based on evidence of habituation of the amygdala to unpleasant stimuli (Hazlett et al., 2012). A greater-than-normal increase in the dACC in the unpleasant condition is also expected reflecting a pattern of increased activity of regulatory regions in schizotypy (Mohanty et al., 2005).

**Aim 4: Correlations between cingulate activation and clinical measures will be examined on an exploratory basis.** The clinical measures used will be the Affective Lability Scale (ALS) and the Affective Intensity Measure (AIM). These analyses will allow us to explore how abnormal functioning of the cingulate may be related to emotion-processing related symptom severity in BPD and SPD. These results are exploratory, but it is predicted that emotion-processing related symptomatology, as measured by the ALS and AIM, will be related to hyper-reactivity to emotional stimuli across the cingulate as well as attenuated habituation of the most anterior regions, failure to engage regulatory regions, and greater-than-normal activation of the PCC when pictures are repeated. In line with the Research Domain Criteria approach of the National Institute of Mental Health (see Insel et al., 2010 for a description), clinical correlations
can be examined across both of the personality disorder groups and also within each group separately. This way, it can be determined whether emotion-processing abnormalities have similar or distinct neurobiological correlates in these disorders.

**METHODS**

**Data Set Information**

The data to be used in the current study were collected as part of an NIMH R01 fMRI grant entitled “Neural substrates of emotion in borderline personality disorder” (PI: Erin Hazlett, Ph.D.; R01 MH073911), which took place at Mount Sinai School of Medicine with the approval of the Mount Sinai Institutional Review Board. Dr. Hazlett has granted permission for use of these de-identified data for the current study. Additionally, the University Integrated Institutional Review Board of CUNY granted approval to use the de-identified data for this study.

**Participants**

Thirty-three patients with BPD, 28 patients with SPD, and 32 healthy controls were included in the analysis (see Table 1 for primary demographics). The groups did not differ significantly in age, gender, or education. All patients met DSM-IV criteria for BPD or SPD and were un-medicated during the time of their fMRI scan; most were never previously medicated. Exclusion criteria included history of schizophrenia, psychotic, or bipolar disorder or current major depressive disorder. Healthy control participants had no Axis I or II DSM-IV diagnosis and no Axis I disorder in any first-degree relative. All participants provided written informed consent in accordance with the Mount Sinai School of Medicine Institutional Review Board guidelines.
Table 1

Sample characteristics by diagnostic group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy controls (n =32)</th>
<th>BPD (n =33)</th>
<th>SPD (n =28)</th>
<th>F, t, or χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [X (s.d.)]</td>
<td>32.8 (9.7)</td>
<td>31.6 (9.1)</td>
<td>35.9 (11.0)</td>
<td>1.49</td>
<td>0.23</td>
</tr>
<tr>
<td>Education [X (s.d.)]*</td>
<td>4.5 (2.8)</td>
<td>3.9 (2.3)</td>
<td>4.0 (2.1)</td>
<td>0.71</td>
<td>0.5</td>
</tr>
<tr>
<td>Gender (n/%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12/38%</td>
<td>13/39%</td>
<td>16/57%</td>
<td>2.79</td>
<td>0.25</td>
</tr>
<tr>
<td>Female</td>
<td>20/62%</td>
<td>20/61%</td>
<td>12/43%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handedness (n%)</td>
<td></td>
<td></td>
<td></td>
<td>0.18</td>
<td>0.84</td>
</tr>
<tr>
<td>Right</td>
<td>29/91%</td>
<td>29/88%</td>
<td>24/86%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>2/6%</td>
<td>4/12%</td>
<td>3/11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1/3%</td>
<td>0/0%</td>
<td>1/0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom Severity [X (s.d.)]</td>
<td>7.8 (1.3)</td>
<td>7.3 (1.2)</td>
<td></td>
<td>1.54</td>
<td>0.13</td>
</tr>
<tr>
<td>Psychoactive Meds</td>
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<td></td>
</tr>
<tr>
<td>Never Medicated (n/%)</td>
<td>-</td>
<td>16/48%</td>
<td>23/82%</td>
<td>7.44</td>
<td>0.006</td>
</tr>
<tr>
<td>Previously Medicated (n/%)</td>
<td>-</td>
<td>17/52%</td>
<td>5/18%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Education=highest degree earned: 1=no high school diploma; 2=GED; 3=high school diploma; 4=technical training; 5=some college, no degree; 6=associate’s degree; 7=bachelor’s degree; 8=master’s degree; 9=MD/PhD/JD/PharmD

Interview and self-report measures

**Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 1996).** The SCID-I is a semi-structured interview used for making major DSM-IV Axis I Diagnoses and is widely used in research settings. It is divided into separate modules corresponding to categories of diagnoses. For all diagnoses, symptoms are coded as present, subthreshold, or absent. Research reports adequate inter-rater reliability, as kappa values have been reported to be between 0.60 and 1.00 (First et al., 1996; Lobbestael, Leurgans, & Arntz, 2011; Zanarini et al., 2000), and inter-rater reliability for the current study was between 0.75 and 0.80 for the different diagnoses.
For each patient, each of the DSM-IV criteria for both personality disorders was rated on a 4-point scale (0=absent; 0.5=somewhat present; 1.0=definitely present/prototypic; 2.0=severe, pervasive). As required for a DSM-IV diagnosis of BPD, these patients met at least five of the nine DSM-IV criteria for BPD with a rating ≥ 0. BPD patients were allowed no more than three SPD criteria with two items rated as 1.0 and one item rated as 0.5. As required for a DSM-IV diagnosis of SPD, these patients met at least five of the nine SPD criteria with a rating ≥ 0. SPD patients were allowed no more than three BPD criteria with two items rated as 1.0 and one item as 0.5 in order to control for comorbidity and/or co-occurring traits. To quantify the level of clinical severity, individual symptom ratings were summed for each diagnostic criterion.

**Structured Interview for DSM-IV Personality Disorders (SIDP; Pfohl, Blum, & Zimmerman, 1997).** The SIDP is a semi-structured interview designed to assess the diagnostic criteria for the 10 personality disorders listed in DSM-IV and takes approximately 60 minutes to administer. The 76 questions are arranged by theme (e.g., work style, interpersonal relationships, emotions, interests, and activities) and each criterion is rated on a scale from 0 to 3. Summed criterion scores are used as an index of personality disorders. It has been shown to have good reliability and validity (Jane, Pagan, Turkheimer, Fiedler, & Oltmanns, 2006). For the present study, intra-class correlations (ICC) were 0.80 for BPD diagnosis, and .73 for SPD diagnosis.

**Affective Lability Scale (ALS; Harvey, Greenberg, & Serper, 1989).** The ALS is a self-report measure of lability of affect. It is a 54-item scale in which participants rate their agreement with statements about their tendency to shift from what they consider to be a normal mood to the affective domains of anger, depression, elation, and anxiety and the tendency to oscillate between depression and elation and between depression and anxiety. Each of the 54
items is rated on a 4-point scale according to how “true” each statement is for them, ranging from “very uncharacteristic” to “very characteristic” of themselves. The total ALS score is the mean of the six individual affect shift scales. It demonstrates a high level of internal consistency ranging from 0.73 to 0.89 and adequate test-retest reliability (Harvey et al., 1989). Internal consistency for the current study was 0.98.

**Affective Intensity Measure (AIM; Larsen & Diener, 1987).** The AIM is a 40-item self-report scale that measures the characteristic strength or weakness with which one experiences emotion. The participant rates each item on a 6-point scale ranging from “never” to “always”. The total AIM score is the mean of the items. This measure demonstrates internal consistency ranging from 0.84 to 0.94, and test-retest reliability of 0.75 to 0.81 (Flett & Hewitt, 1995; Larsen, Diener, & Emmons, 1986). In the present study, internal consistency was 0.83.

**Functional and structural MRI acquisition**

The MRI scan procedure was conducted on a Siemens-Allegra head-dedicated 3T scanner and included a T2, EPI, and T1-weighted structural MP-RAGE (Magnetization-Prepared-Rapid-Gradient-Echo scan). The T2 involved a Turbospinecho sequence (TE = 99 msec, TR = 5760, slice thickness = 3 mm/skip 1 mm, field of view (FOV) = 21 cm, matrix 256 x 256, 32 slices). EPI images were acquired with a BOLD-EPI sequence (42-axial slices, 2.5 mm thick, skip = 0.8 mm (33%), TR = 3000 msec, TE = 27 msec, flip angle = 85°, FOV = 210 mm, matrix = 64 x 64). For high-resolution-structural-images that allowed accurate anatomical tracing of the cingulate, we acquired T1-weighted structural magnetization-prepared rapid gradient echo (MP-RAGE) imaging (208 slices for whole brain; axial acquisition, 0.82 mm slice thickness, TR = 2500 msec, TE = 4.38 msec, TI = 1100 msec, flip angle = 8°, FOV = 210 mm, matrix size = 256 x 256 x 208).
Event-related fMRI affective picture processing task

During the fMRI scan, participants viewed unpleasant, neutral and pleasant pictures from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008), a collection of photographic images that have been shown to induce positive, negative, or neutral affective states (Lang et al., 2008). Ninety-six intermixed unpleasant, neutral, and pleasant pictures were presented. Each of the 96 pictures were presented twice within their respective run for a total of 192 picture trails. Each trial was 8 seconds long and included either (a) the presentation of a picture (6 seconds) followed by a 3-choice button press response prompt (for 2 seconds) or (b) a fixation cross (8 seconds). The presentation of either a picture or fixation cross was semi-randomized with the number of consecutive trials varying from 1-6 for pictures and 1-3 for fixation trials. Each run contained 24 unique pictures (8 unpleasant, 8 neutral, and 8 pleasant) which were repeated once (48 picture events) and 16 non-picture (fixation cross) events for a total of 64 contiguous trails per run. The total scan time was 38-minutes, 12-seconds which was divided into four runs with 30 seconds before and 31 seconds after each run.

The pictures were predominantly social in nature including faces and social interactions. The unpleasant and pleasant pictures were matched based on the picture ratings from the standardized IAPS manual for arousal, and they were equally divergent from neutral in terms of valence. The neutral pictures were matched across each of the four runs on arousal and valence. All participants viewed the same stimulus sequence.

Participants were instructed to attend to the pictures and think about their meaning for them personally. Immediately following the offset of each picture, a cartoon-like picture of a right hand with the pointer finger labeled as pleasant, middle finger labeled as neutral, and the ring finger labeled as unpleasant appeared for 2 seconds. Once the participants saw the hand
prompt, they made a 3-choice response with their right hand using BrainLogics fiber optic button system. The responses helped ensure that the participants were engaged in the task.

Immediately following the scan, participants viewed the same 96 pictures on a computer and rated them using the Self-Assessment Manikin scale (SAM; 9 point-scale).

**Image Processing**

FSL’s fMRI Expert Analysis Tool was used to process the images. The BOLD data were preprocessed with motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002), non-brain removal using BET (Smith, 2002), spatial smoothing (FWHM=5 mm), and a high-pass temporal filter (cutoff=70 sec). The MP-RAGE and EPI images were co-registered with a 7-degrees-of freedom (DOF) linear transformation followed by alignment to the MNI brain template using a 12-DOF linear fit.

**Cingulate Tracing on MRI**

The left and right anterior and posterior cingulate were manually traced on axial MR images for each subject, blind to diagnosis. Inter-tracer reliability was confirmed (inter-observer intraclass correlation coefficient for the anterior cingulate = 0.85 and posterior cingulate = 0.84). Methods have been published in detail elsewhere (Haznedar et al., 2004; Segal et al., 2010). The ACC was operationally defined by outlining beginning at the deepest recess of the cingulate sulcus, moved medially, and then in an inferior direction until reaching the callosal recess. Tracing began ventrally with the plane showing the appearance of the cingulate sulcus in place of the gyrus rectus and ended dorsally with the plane showing the disappearance of the corpus callosum (Figure 2). Outlining of the posterior cingulate started at the axial plane on which the splenium of the corpus callosum could be visualized. Outlining began from the recess of the
gyrus adjacent to the corpus callosum and followed the gray matter and cerebrospinal fluid in the medial part. The gyrus was followed until the hilt of the recess, and a straight line was drawn to connect the two recesses (Figure 2). Tracing was carried out dorsally, and at the axial plane where the corpus callosum disappears and the anterior and posterior cingulate merge, the x-y coordinates of the merging point were identified. These coordinates were then designated as the margins of the anterior cingulate and the posterior cingulate on higher axial planes (Haznedar et al., 2004). Defining the posterior cingulate with the deepest sulcus in the parietal and the occipital lobes excludes posterior cingulate Brodmann areas 30 and 31; however, this approach has the advantage of excluding medial-parietal and medial-occipital cortex areas such as the precuneus. Co-registration of the structural MRI and fMRI allows obtainment of BOLD response in the ACC and PCC. To determine mean BOLD response for each ACC sub-region, the ACC was divided into three segments, Brodmann Area 25 (sgACC), 24 (pgACC), and 24’ (dACC), based on proportions derived from the Talairach-Tournoux atlas (22%, 33%, and 44%, respectively; Talairach and Tournoux, 1988; Figure 3).
Figure 2. Tracing the Cingulate Cortex

The ACC was operationally defined by outlining beginning at the deepest recess of the cingulate sulcus, moved medially and then posterior direction until reaching the callosal recess. The two recesses were connected to each other with a straight line. Outlining the PCC began at the axial plane on which the splenium of the corpus callosum could be visualized. Outlining started from the recess of the gyrus adjacent to the corpus callosum and followed the gray matter in the medial portion. The gyrus was followed until the hilt of the recess and a straight line was drawn to connect the two recesses. (A) Mid-section of the sgACC. (B) Mid-section of the pgACC. (C) Midsection of the dACC. (D) Mid-section of PCC (BA 29). (E) Mid-section of PCC (BA 23).
a=anterior cingulate gyrus, b=cingulo-frontal transition cortex (BA 32), c=caudate nucleus, d=BA 10, p=putamen, cc=corpus callosum, t=thalamus, pc=posterior cingulate, pr=precuneus.
Figure 3. Segmenting the Cingulate

The ACC was segmented to approximate the sgACC (blue), pgACC (pink), and dACC (yellow) based on proportions derived from the Talairach-Tournoux atlas. The red portion represents the PCC.
Data analysis

Mixed-design analysis of variance (ANOVA) will be used to address Aims 1-3. For both the ACC and PCC, the independent variable will be Diagnosis (Healthy Control vs. BPD vs. SPD) and the dependent variable will be BOLD response. For the ACC, repeated measures will be Anteroposterior Segment (sgACC, pgACC, and dACC), Picture-Type (pleasant, unpleasant, and neutral), and Picture-Repetition (novel and repeated). Multivariate $F$-values (Wilks’ Lambda) or univariate $F$-values with Huynh-Feldt adjusted $p$-values will be reported. Fisher’s LSD test will be used to follow up significant interactions.

For Aim 1: A significant Diagnosis $\times$ Picture-Type (unpleasant, neutral, and pleasant) interaction is expected for the ACC and the PCC which will reveal a. greater BOLD response in the ACC and PCC in BPD patients compared to healthy controls for all conditions (pleasant, unpleasant, and neutral), and b. greater BOLD response in the ACC and PCC in SPD compared to healthy controls for the unpleasant condition only.

For Aim 2: A significant Diagnosis $\times$ Anteroposterior Segment (sgACC, pgACC, dACC) $\times$ Picture-Type (unpleasant, neutral, and pleasant) interaction is expected which will reveal a. greater BOLD response in BPD patients compared to healthy controls in the pgACC in the pleasant condition and in the sgACC and dACC in the unpleasant and neutral condition, and b. greater BOLD response in the sgACC and dACC in SPD patients compared to healthy controls in the unpleasant condition.

For Aim 3: A significant Diagnosis $\times$ Anteroposterior Segment (sgACC, pgACC, dACC) $\times$ Picture-Type (unpleasant, neutral, and pleasant) $\times$ Picture-Repetition (novel and repeated) interaction effect for the ACC and a significant Diagnosis $\times$ Anteroposterior Segment (sgACC, pgACC, dACC) $\times$ Picture-Type (unpleasant, neutral, and pleasant) $\times$ Picture-Repetition
(novel and repeated) interaction effect for the PCC are expected which will reveal a. a lower decrease in BOLD response from novel to repeated pictures in the sgACC and pgACC in BPD patients compared to SPD patients and healthy controls in all picture-type conditions, b. a lower increase in BOLD response from novel to repeated pictures in the dACC in BPD patients compared to SPD patients and healthy controls in all pictures-type conditions, c. a greater increase in BOLD response in the PCC from novel to repeated pictures in BPD patients compared to SPD patients and healthy controls in all picture-type conditions, and d. a greater increase in BOLD response in the dACC in SPD patients compared to healthy controls and BPD patients in the unpleasant condition.

For **Aim 4**: To examine the exploratory aim about individual differences, Pearson’s correlation coefficients will be used to examine associations between BOLD response in the cingulate and clinical measures. In order to limit the number of correlations conducted, only the cingulate sub-regions that were found to significantly differ among diagnostic groups will be used in the analysis. While this analysis is exploratory in nature, the following predictions are made: Higher scores on the ALS and AIM will be associated with a. greater BOLD response in the ACC (and sub-regions) and PCC (averaged over picture-type and repetition), and b. a smaller decrease in BOLD response in the sgACC and pgACC, a smaller increase in BOLD response in the dACC, and a greater increase in BOLD response of the PCC when pictures are repeated.

**RESULTS**

**Preliminary Analyses**

Demographic data for the total sample are included in Table 1. The diagnostic groups did not significantly differ on age, sex, education, or handedness ($p > 0.05$). One participant in the BPD group had numerous BOLD response values greater than 8-10 standard deviations from the
mean, presumably due to measurement error of the MRI. This participant was excluded from the analysis. Descriptive statistics are presented in Table 2. Normality of the data was assessed using the Kolmogorov-Smirnov test. BOLD response values for each cell (indicated in Table 2) were normally distributed (Kolmogorov-Smirnov test, $p > 0.05$), with two exceptions: BOLD response for novel neutral pictures and repeated pleasant pictures in the sgACC of the SPD group. Transformation of the data was not possible because when the transformation was applied to the other diagnostic groups (already normally distributed), many became non-normal. ANOVA is considered fairly robust to deviations from normality, and only 2 of 54 cells for the ACC analysis violated the normality distribution; therefore, the analysis was carried out with no transformation.
### Table 2

Mean (SD) for BOLD response and clinical measures by diagnostic group

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls</th>
<th>BPD Patients</th>
<th>SPD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 32 )</td>
<td>( n = 32 )</td>
<td>( n = 28 )</td>
</tr>
<tr>
<td>( \text{sgACC (BOLD)} )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleasant</td>
<td>-0.02(0.72)</td>
<td>-0.28(0.78)</td>
<td>-0.04(0.81)</td>
</tr>
<tr>
<td>Neutral</td>
<td>-0.22(0.89)</td>
<td>0.05(0.9)</td>
<td>-0.49(1.34)</td>
</tr>
<tr>
<td>Unpleasant</td>
<td>-0.32(0.81)</td>
<td>-0.41(0.61)</td>
<td>-0.21(0.81)</td>
</tr>
<tr>
<td>Repeated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleasant</td>
<td>0.14(0.75)</td>
<td>0.11(0.65)</td>
<td>0.32(1.21)</td>
</tr>
<tr>
<td>Neutral</td>
<td>-0.03(0.53)</td>
<td>0.37(0.66)</td>
<td>0.2(0.95)</td>
</tr>
<tr>
<td>Unpleasant</td>
<td>0.17(0.74)</td>
<td>0.24(0.67)</td>
<td>0.04(0.63)</td>
</tr>
<tr>
<td>( \text{pgACC (BOLD)} )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleasant</td>
<td>-0.04(0.73)</td>
<td>-0.19(0.78)</td>
<td>0.03(0.83)</td>
</tr>
<tr>
<td>Neutral</td>
<td>-0.23(1)</td>
<td>0.16(0.91)</td>
<td>-0.35(1.08)</td>
</tr>
<tr>
<td>Unpleasant</td>
<td>-0.3(0.92)</td>
<td>-0.25(0.74)</td>
<td>-0.01(0.69)</td>
</tr>
<tr>
<td>Repeated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleasant</td>
<td>0.16(0.93)</td>
<td>0.12(0.81)</td>
<td>0.36(1.17)</td>
</tr>
<tr>
<td>Neutral</td>
<td>-0.03(0.6)</td>
<td>0.32(0.64)</td>
<td>0.16(0.96)</td>
</tr>
<tr>
<td>Unpleasant</td>
<td>0.08(0.69)</td>
<td>0(0.86)</td>
<td>-0.1(0.76)</td>
</tr>
<tr>
<td>( \text{dACC (BOLD)} )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleasant</td>
<td>-0.01(0.6)</td>
<td>-0.18(0.7)</td>
<td>0.1(1.11)</td>
</tr>
<tr>
<td>Neutral</td>
<td>-0.21(0.98)</td>
<td>0.16(0.95)</td>
<td>-0.36(1.14)</td>
</tr>
<tr>
<td>Unpleasant</td>
<td>-0.27(1)</td>
<td>-0.27(0.83)</td>
<td>0.08(0.65)</td>
</tr>
<tr>
<td>Repeated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleasant</td>
<td>0.24(0.69)</td>
<td>0.14(0.78)</td>
<td>0.27(1.14)</td>
</tr>
<tr>
<td>Neutral</td>
<td>-0.02(0.58)</td>
<td>0.39(0.79)</td>
<td>0.02(0.89)</td>
</tr>
<tr>
<td>Unpleasant</td>
<td>-0.1(0.8)</td>
<td>-0.15(0.73)</td>
<td>-0.21(0.7)</td>
</tr>
<tr>
<td>( \text{PCC (BOLD)} )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleasant</td>
<td>0.12(0.7)</td>
<td>-0.17(1.02)</td>
<td>0.04(0.96)</td>
</tr>
<tr>
<td>Neutral</td>
<td>-0.35(0.94)</td>
<td>-0.1(1.03)</td>
<td>-0.62(0.71)</td>
</tr>
<tr>
<td>Unpleasant</td>
<td>-0.15(0.74)</td>
<td>0.01(1.12)</td>
<td>0.26(0.69)</td>
</tr>
<tr>
<td>Repeated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleasant</td>
<td>0.11(0.72)</td>
<td>0.16(0.69)</td>
<td>0.39(0.99)</td>
</tr>
<tr>
<td>Neutral</td>
<td>-0.07(0.71)</td>
<td>0.09(1.01)</td>
<td>-0.09(0.73)</td>
</tr>
<tr>
<td>Unpleasant</td>
<td>0.16(0.98)</td>
<td>0.25(0.7)</td>
<td>-0.01(0.78)</td>
</tr>
</tbody>
</table>

\( \text{AIM}^a \)

\begin{align*}
\text{AIM}^a & = 3.32(0.44) \\
\text{ALS}^b & = 0.42(0.38) \\
\end{align*}

\( ^a \text{missing for 2 healthy controls and 1 BPD patient} \)

\( ^b \text{missing for 2 healthy controls} \)
Hypothesis Testing

Aim 1: To examine diagnostic group differences in the activation of the cingulate during presentation of pleasant, unpleasant, and neutral emotional pictures.

Results: A Diagnosis × Picture-type interaction effect of BOLD response in the ACC was significant (\(F[3.9,175.4] = 2.42; \ p = 0.05\); partial \(\eta^2 = 0.052\); Huynh-Feldt; Figure 4). The effect showed that the BPD patients had significantly higher BOLD response to neutral pictures in the ACC compared to healthy controls (Fisher’s LSD, \(p = 0.005\); Cohen’s \(d = 0.64\)) and SPD patients (Fisher’s LSD, \(p = 0.005\); Cohen’s \(d = 0.66\)). The SPD patients had higher activation during the pleasant and unpleasant conditions, although these comparisons did not reach significance. The interaction effect for the PCC did not reach significance (\(F[4, 176] = 1.34; \ p = 0.26\); Wilks’ Lambda).

Figure 4
BOLD response in the ACC by picture-type. Significant post-hoc Fisher’s LSD tests, \(p < 0.05\), are noted and standard error bars are provided in the graph.
Aim 2: To examine the location of diagnostic group differences in activation within three sub-regions of the ACC.

Results: The Diagnosis × Picture-type × Anteroposterior segment interaction effect of BOLD response in the ACC did not reach significance ($F[7.0, 312.8] = 0.42; p = 0.88$; Huynh-Feldt).

Aim 3: To examine diagnostic group differences in change of activation of the cingulate cortex between initial and repeated presentation of emotional pictures.

Results: None of the interactions with group and picture-repetition reached significance in the ACC or PCC.

Aim 4: Correlations between cingulate activation and clinical measures will be examined on an exploratory basis.

Results: In accordance with the data analytic plan, correlations with the clinical measures were conducted only for cingulate regions found to have irregular activity in the patient groups. Therefore, Pearson’s correlations between ACC BOLD activation for pleasant, neutral, and unpleasant pictures and the affective measures (ALS and AIM) were conducted (Table 3). Correlational analyses showed that across all subjects, greater ACC BOLD activation during neutral pictures was associated with higher affective intensity ($r = 0.21, p = 0.048$) and lability ($r = 0.24, p = 0.023$; measured by the AIM and ALS, respectively). ACC BOLD activation to neutral pictures was positively associated with the AIM and ALS for the BPD group ($r = 0.33, p = 0.070$ and $r = 0.33, p = 0.065$, respectively) but negatively associated for the SPD group ($r = -0.18, p = 0.36$ and $r = -0.25, p = 0.20$, respectively).
Table 3

Correlations between ACC BOLD response and clinical measures

<table>
<thead>
<tr>
<th></th>
<th>All Subjects</th>
<th>BPD only</th>
<th>SPD only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AIM</td>
<td>ALS</td>
<td>AIM</td>
</tr>
<tr>
<td><strong>ACC BOLD response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleasant</td>
<td>-0.11</td>
<td>-0.18**</td>
<td>-0.17</td>
</tr>
<tr>
<td>Neutral</td>
<td>0.21*</td>
<td>0.24*</td>
<td>0.33**</td>
</tr>
<tr>
<td>Unpleasant</td>
<td>0.01</td>
<td>-0.10</td>
<td>-0.14</td>
</tr>
</tbody>
</table>

*significant at p < 0.05
**significant at p < 0.10

Exploratory Analysis

The Diagnosis x Picture-Type interaction effect examined BOLD response averaged over a period of 33 seconds. BPD is characterized by a strong initial reaction and a slower return to baseline following emotional arousal. Time (3s, 6s, 9s,…33s) was entered as a factor in our ACC analysis to examine these time-dependent features of arousal, particularly for the neutral condition in which BPD patients demonstrated substantially increased ACC activation. It was predicted that the BPD patients would show more sustained arousal and a slower return to baseline over the 33-second period compared to the other groups.

The analysis did reveal a significant Diagnosis x Picture-Type x Picture-Repetition x Time interaction effect of BOLD response in the ACC (F[40, 140] = 1.97; p = 0.03; partial η² = 0.027; Huynh-Feldt; see Figure 5).
Figure 5
The top graph represents ACC activity for novel pictures and the bottom graph is repeated pictures. Most notable was the widespread heightened activation of the ACC in the BPD patient group compared to the other groups in the neutral condition. Healthy controls demonstrated ACC deactivation for neutral pictures. Activity eventually rose back to baseline levels. In contrast, the BPD group activated the ACC, and activity largely increased across the 33 second time span for the neutral condition. ACC activation was even greater in the BPD patients when pictures were repeated, with a large peak of activation well above the other groups. Also noteworthy was the high peak of activation of the SPD patients in the novel unpleasant condition. BOLD response in the SPD patients was significantly higher than the other two groups when unpleasant pictures were first presented. This pattern was not observed when the pictures were repeated, with activation dropping even lower than normal.
DISCUSSION

The aim of this study was to compare BOLD activation and habituation in the cingulate cortex during novel and repeated emotional and neutral pictures in three groups: healthy controls, individuals with borderline personality disorder (BPD), and individuals with schizotypal personality disorder (SPD). Emotional impairments are central features of BPD and SPD, and the cingulate is a potential neural substrate of abnormal emotional reactivity and habituation. There are two key findings from this study. First, BPD patients exhibited significantly greater activity in the anterior cingulate cortex (ACC), compared to healthy controls and SPD patients, during the presentation of neutral pictures. Heightened activity in the BPD group persisted across the initial and repeated presentation of neutral pictures. Second, SPD patients showed greater activity in the ACC, compared to healthy controls and BPD patients, during the initial presentation of unpleasant pictures, but activity appeared to normalize when the pictures were repeated. These findings are discussed in detail below.

Anterior Cingulate Cortex Activation

The anterior portion of the cingulate is thought to be involved in the generation and regulation of emotional responses and is therefore an important region of interest in the study of emotion processing. Findings of diagnostic differences in ACC activation during the presentation of emotional pictures are partially consistent with the hypotheses proposed. Specifically, the results are congruent with the prediction that BPD patients would exhibit heightened response in the ACC for neutral stimuli compared to healthy controls and SPD patients. These results are also consistent with previous findings of increased activation of the ACC (Niedtfeld et al., 2010) and other limbic structures (Donegan et al., 2003) in BPD patients when neutral pictures are presented. BPD is characterized by prolonged emotional responses and
a slower return to baseline following emotional arousal (Linehan et al., 1993). To assess whether these time-dependent features in arousal were reflected in ACC activity in BPD patients, BOLD response across 12 time points, 3 seconds apart, was examined in an exploratory basis. This analysis revealed that BPD patients exhibited fairly consistent activation across all time points during the presentation of novel neutral pictures, with no clear return to baseline.

It was expected that BPD patients would show heightened ACC response for neutral stimuli due to a tendency of these patients to interpret neutral or ambiguous stimuli as negative (Mitchell, Dickens, & Picchioni, 2014). However, our BPD sample did not exhibit heightened activity in the ACC during the presentation of negative stimuli; this effect was unique to the neutral condition. If heightened activation to neutral stimuli was due to the interpretation of neutral stimuli as negative, then activity in response to unpleasant and neutral stimuli should be similar. Furthermore, in a previous study of these patient groups, the BPD patients exhibited a pattern of greater amygdala BOLD activation to the emotional, both unpleasant and pleasant, but not the neutral pictures when they were repeated. Increased arousal, as indicated by heightened amygdala activation, was restricted to the emotional, but not neutral, conditions in this patient group. Therefore, it is unlikely that heightened ACC activation in the neutral condition simply reflects heightened arousal but is more likely a consequence of increased cognitive or attentional processing.

An alternative interpretation of these findings is that heightened ACC activity during the neutral condition reflects a pronounced difficulty in interpreting emotionally ambiguous material. The ACC, particularly the dACC, has been implicated in the processing of ambiguous stimuli (Keri, Decety, Roland, & Gulyas, 2004; Nomura et al., 2003) and ambiguous decision-making (Krainsk, Wilson, Arbuckle, Castellanos, & Milhan, 2006). While activation was greater
than normal across the entire ACC in the neutral condition, activation in the dACC was the highest of all the ACC sub-divisions in the BPD group. Alternatively, heightened activation of the ACC could also reflect an increased focus of attention on this stimulus type in the BPD patients due to its problematic nature. Difficulty evaluating ambiguous faces has been noted in BPD patients. They take longer in the appraisal of ambiguous faces (Fertuck, Grinband, & Stanley, 2013), are less accurate at recognizing neutral facial expressions, and show a general tendency to assign emotion to neutral faces (Daros, Uliaszek, & Ruocco, 2014).

Linehan’s biosocial theory proposes that BPD develops out of an individual’s genetic predisposition to emotional sensitivity and dysregulation combined with an invalidating childhood environment (Linehan, 1993). An invalidating environment is characterized by an intolerance toward the expression of emotion which may lead to difficulties in recognizing and labeling one’s own emotions (Linehan, 1993). Relying on one’s own internal processes to evaluate environmental stimuli with no obvious external emotional cues may be particularly problematic for this population. Increased recruitment of the ACC in the neutral condition potentially reflects a difficulty in processing stimuli that lacks clarity in their emotional meaning and represents a potential neurobiological correlate of difficulties in evaluating ambiguous faces that is reported in BPD.

However, it is interesting to note that this BPD sample did not differ from the other groups in their self-reported ratings of the neutral stimuli. These findings suggest an abnormality in processing neutral stimuli on a neural level that may not translate to subjective experience. This disconnect between physiological arousal and self-report has been reported before, specifically for unpleasant emotional stimuli (Hazlett et al., 2007; Herpertz et al., 2001; Koenigsberg, Fan, et al., 2009). The discrepancy in physiological arousal and self-reported
arousal may reflect heightened alexithymia, an inability to read emotions (including one’s own), which has been reported in these patients (New et al., 2012). The findings of this study are consistent with a previously reported mismatch of physiological response and subjective experience and expand these findings to neutral stimuli as well.

The correlational analysis complemented the ACC findings, with higher levels of affective lability (the tendency to shift moods quickly) and intensity (the strength with which one experiences emotion) associated with higher ACC activation in the neutral condition across all subjects. Affective lability and intensity are prominent features of the emotional dysfunction observed in BPD patients. That these features are associated with heightened activity of the ACC for neutral pictures bolsters our findings from the analysis of group differences. Interestingly, when the correlations were performed with only the BPD patient group, these associations became even larger, although the significance was only at a trend level due to the smaller sample size. On the other hand, the SPD patients exhibited the opposite association; ACC activation for neutral pictures was inversely associated with affective lability and intensity, although the correlations did not reach significance. These findings indicate that the positive relationship between ACC activation during neutral pictures and affective lability and intensity may be a neurobiological correlate distinct to BPD patients.

Unexpectedly, ACC activation in BPD patients during the presentation of unpleasant pictures did not differ from the other groups, contrary to the hypotheses proposed and previous findings of enhanced ACC activation for negatively-valenced pictures (e.g., Niedtfeld et al., 2010; Schnell & Herpertz, 2007) and unresolved life events (Beblo et al., 2006) in BPD patients. However, research has been inconsistent in this area, with others studies reporting a greater deactivation of the ACC in BPD patients when listening to personalized scripts describing
abandonment and abuse (Schmahl et al., 2003), and others finding no differences for passive viewing of affective pictures (Herpertz et al., 2001; Koenigsberg, Siever, et al., 2009) and during an emotion discrimination task (Guitart-Masip et al., 2009). Findings in the ACC across studies of negative emotion processing have been highly discrepant, perhaps due to differences in methodology (e.g., audio versus visual stimuli, cognitive-emotion tasks versus passive viewing) and sample characteristics (e.g., medication status of patients, clinical severity of patients, and diagnostic co-morbidity). The lack of findings for unpleasant pictures, therefore, was unexpected but not unusual given the inconsistency of previous findings.

Additionally, the current BPD sample did not demonstrate heightened activity in the ACC when presented with pleasant pictures. Previous findings have been mixed with regards to reactivity to pleasant stimuli in BPD patients, with some reports of decreased physiological, neural, and self-reported response to pleasant stimuli (Hazlett et al., 2012; Herpertz et al., 2000) and other reports of increased limbic activation during the presentation of pleasant stimuli (Baskin-Sommers et al., 2015; Donegan et al., 2003).

One interpretation of the lack of findings for unpleasant and pleasant pictures is that this BPD sample is not hyper-reactive to the emotional stimuli in this study. However, as mentioned above, a previous study of these patient groups showed that these BPD patients exhibited a pattern of greater amygdala BOLD activation to both emotional picture conditions, unpleasant and pleasant, when the pictures were repeated. Therefore, this patient group does appear to display heightened arousal in response to the emotional pictures, but this effect is not reflected in higher ACC activation. Heightened ACC activation to emotional stimuli has not been consistently reported in this population, and, therefore, the ACC may not be an accurate indicator of increased emotional arousal in response to the presentation of affective pictures in BPD.
On the other hand, as predicted, the SPD group did exhibit higher activation for the unpleasant pictures. This finding did not reach significance in our planned analyses. However, exploratory analyses revealed that SPD patients exhibited a significantly higher peak of activation in the ACC for novel unpleasant pictures compared to the other groups. These findings are consistent with previous research that indicates hyper-reactivity to aversive stimuli in children at risk of developing SPD (Raine et al., 2002). They also mirror previously published findings in this sample which showed a similar pattern of heightened amygdala activation for novel unpleasant pictures (Hazlett et al., 2012). The interpretation of heightened activation in the whole ACC during the presentation of unpleasant emotional pictures is challenging given the functional diversity of this structure in affective processing. On the one hand, the ACC is involved in the assessment of the salience of stimuli and the production of somatic and autonomic emotional responses, and increased involvement of the ACC may reflect a heightened affective arousal. This is consistent with the findings of increased amygdala activation during unpleasant pictures previously reported in this sample (Hazlett et al., 2012). Alternatively, as a region involved in the regulation of emotion (Etkin et al., 2011; Ochsner & Gross, 2005), increased ACC activation may indicate a heightened recruitment of regulatory processes. Abnormally high amygdala activation for unpleasant pictures (Hazlett et al., 2012) may increase the demand for inhibition via connections with the ACC (Etkin et al., 2011). Either way, these findings lend support to the notion that SPD patients are hyper-reactive to aversive stimuli, and increased ACC activation either contributes to this heightened arousal or reflects an effort to regulate it. High levels of anxiety and paranoia, both features of SPD, are associated with hyper-vigilance to aversive stimuli (Etkin & Wager, 2007; Green & Phillips, 2004) and may help to
explain heightened limbic reactivity to novel unpleasant pictures in this group, although this hypothesis needs to be further examined.

**Posterior Cingulate Cortex Activation**

Unexpectedly, the planned analyses revealed no significant diagnostic effects in the PCC, contrary to our proposed hypotheses and previous reports of enhanced activation of the PCC (Koenigsberg, Siever et al., 2009; Ruocco et al., 2013; Schulze et al., 2016). Again, lack of findings may be due to sample and methodological differences. For example, medication status and dissociative states are both factors that have been shown to modulate functional neural activity in BPD patients and could contribute to discrepancy in results (Krause-Utz et al., 2014; Schulze et al., 2016). Furthermore, the two meta-analyses which reported increased PCC activation in BPD patients (Ruocco et al., 2013; Schulze et al., 2016) included studies which utilized emotion tasks with a cognitive component whereas the current study simply presented emotional pictures with no cognitive task. The current findings did not support the hypothesis that BPD and SPD patients exhibit abnormal PCC activation during the simple presentation of emotional and neutral pictures.

**Habitation**

The planned analyses did not reveal any interaction effects with picture-repetition. However, the exploratory analysis which included time as a factor did reveal diagnostic differences in ACC activation for novel versus repeated pictures. As described above, the SPD patients exhibited a greater peak of activation in the ACC compared to the other two groups for novel unpleasant pictures. However, this effect appeared to normalize when pictures were repeated, with the SPD patients exhibiting ACC activation similar to, or even lower than, the
healthy controls. These findings of hyper-activation to novel pictures which normalizes when the pictures are repeated mirror previously published findings in this sample which showed a similar pattern of amygdala activation for novel and repeated unpleasant pictures (Hazlett et al., 2012), again supporting the idea that increased activation of the ACC in this group is likely reflective of heightened arousal in this group. Normalization of ACC activation could indicate decreased salience of the stimuli due to repeated presentation, leading to less response in the ACC. Alternatively, decreased activation could reflect successful inhibition of the emotional response. Abnormally high amygdala activation for novel unpleasant pictures (Hazlett et al., 2012) may increase the demand for inhibition via connections with the ACC initially (Etkin et al., 2011). However, as activity in the amygdala decreases upon repeated presentation of the picture, there is less inhibitory demand. These findings lend support to the notion that SPD patients are hyper-reactive to aversive stimuli but do successfully regulate this exaggerated response when the stimuli are repeated. The normalization of this hyper-reactivity upon repeated presentation suggests that affective regulatory processes are intact.

On the other hand, for novel neutral pictures, BPD patients exhibited fairly consistent activation across all time points, with no clear return to baseline. Additionally, when the neutral stimuli were repeated, the BPD patients exhibited even higher levels of activation of the ACC, as evidenced by a large mid-time-series peak. ACC activation did not return to “normal” levels upon repeated presentation of the stimuli as it did in the SPD patients for unpleasant stimuli. The increase in activation from novel to repeated presentation suggests that the ambiguity of this type of stimuli may become even more problematic as it is encountered again.
Study Implications

The current study provides evidence that BPD patients exhibit an exaggerated ACC response when exposed to neutral stimuli, a response that does not normalize upon repeated presentation of the stimuli and may represent a neural substrate of impaired social cognition. These results, combined with previous findings of behavioral impairments in processing ambiguous social stimuli (e.g., Daros, Uliaszek, & Ruocco, 2014; Fertuck, Grinband, & Stanley, 2013) highlight social cognition as a potentially important domain of dysfunction in BPD patients. Impaired social cognition has been previously linked to BPD symptomatology (Fonagy et al., 1996), and impaired interpersonal functioning can trigger suicidal and self-injurious behavior in this population (Brodsky et al., 2006). Three symptom clusters have been identified in BPD: affective dysfunction, behavioral dysfunction, and disturbed relatedness (Sanislow et al., 2002). However, disturbed relatedness has received the least amount of attention of these three symptom clusters in BPD research (Preissler et al., 2010). Current theories of BPD are largely focused on heightened emotionality as a central feature of this disorder. For example, Linehan’s biosocial theory emphasizes emotion dysfunction, particularly heightened emotional arousal and dysregulation, as the core feature of BPD and the primary source of behavioral and interpersonal impairments in these patients. In terms of treatment, this approach primarily endorses the development of skills to tolerate and regulate these strong emotions and to cope with stressors that may trigger such a response (Linehan, 1993). However, in light of the current findings, previous findings of social cognitive impairments, and the significance of disturbed relatedness in the symptomatology of BPD, the current theoretical framework and treatment approach of this disorder may benefit from more thoroughly incorporating social cognitive dysfunction as a central component of this disorder.
One treatment approach that may more effectively address impairments in social cognition and interpersonal relatedness is mentalization-based treatment (MBT). MBT places the loss of mentalizing, which can be described as understanding the mental states underlying one’s own actions and those of others, as a core feature of this disorder (Bateman & Fonagy, 2010). The treatment aims to develop the patient’s skill of mentalizing, an approach which may help the patient to process and manage more effectively ambiguous social situations outside the therapeutic setting. Another approach which may also be useful in this regard is transference-focused psychotherapy (TFP), a psychodynamic-based treatment for personality disorders based on Kernberg’s object relations model. TFP focuses on understanding the relationship between therapist and patient as a way of helping the patient understand his or her emotions and interpersonal problems (Clarkin, Levy, & Schiavi, 2005). Insights gained through the therapeutic relationship can then be applied to real world situations. TFP, therefore, may provide a safe environment for the patient to practice managing ambiguous social situations and interactions. Regardless of the approach, it may be important to incorporate practice in the identification and processing of neutral or ambiguous situations and facial expressions in the therapeutic setting.

The BPD findings also have methodological implications for the analysis of fMRI data. Event-related fMRI during the passive viewing of emotional faces or scenes is a common approach to examining emotion processing in BPD. Researchers often contrast neural activation during emotion stimuli versus neutral stimuli to subtract out the effects of simply looking at complex scenes or faces when analyzing fMRI data. However, the current findings of heightened ACC activation to neutral pictures combined with previous evidence of a tendency to assign emotion to neutral stimuli (Daros et al., 2014) indicates that BPD patients may not
interpret neutral pictures as neutral. The use of a negative-neutral or positive-neutral contrast in BPD patients may call into question the validity of the findings.

**Study Limitations**

Despite numerous strengths of the current study, such as the inclusion of two personality disorder groups and the use of manually-traced ROIs, a few methodological limitations should be noted. Manually outlining the ACC and PCC individually on each subject offers a level of precision and anatomical relevance not available when using other methods. However, the current tracing method relies on sulcal landmarks to define the boundaries of the ACC and PCC. While histological markers would be more desirable for outlining the boundary of the cingulate, this is not possible given the resolution of the MR images. The use of sulcal markers is a reasonable substitute for histological markers as it is easily visualized and reliably identified. Also, the lack of anteroposterior segments effects in the ACC raises questions about the accuracy of our parcellation scheme. The sub-regions of the ACC do not have clear anatomical boundaries, but the transition from one region to the next is gradual (Vogt 2009). Therefore, sub-dividing the ACC based on histological markers is not possible and must be approximated. The current parcellation scheme was based on proportions derived from the Talaraich atlas (Talairach & Tournoux, 1988) which divided the ACC into three sub-regions that roughly correspond to the sgACC, pgACC, and dACC.

A further limitation of the current study is that the images were not parsed out into specific basic emotions (e.g., fear, disgust, etc.) but were grouped solely based on valence. The hypotheses regarding differences in BOLD response in the sub-regions of the ACC were based on a model of distinctive regional activation of the ACC in the processing of discrete emotions (Vogt, 2005). Furthermore, previous findings have suggested the BPD patients demonstrate
different neural activation to distinct forms of negatively-valenced stimuli. For example, activation in the sgACC was observed to be decreased during fear processing but increased during anger processing in BPD patients (Minzenberg et al., 2007). Therefore, grouping all negatively-valenced images together could account for the failure of the current study to find group differences in sub-region activation. Future work may address this issue by parsing out images into more specific categories (e.g., sadness, fear, and anger) versus using a general unpleasant category and examining activation differences according to more specific picture types.

An additional limitation of the current study is that the functional diversity of the ACC makes interpretation of the results challenging. The hypotheses of the current study assumed that activation of the cingulate in response to emotional images would reflect heightened arousal in the individual. However, given the findings of differences in ACC activation for neutral but not emotional pictures in BPD patients, it is more likely that these activation differences reflect greater cognitive processing versus arousal. Perhaps BPD patients give more attention to, or require greater neural processing of, neutral or ambiguous pictures compared to healthy controls because their content is particularly problematic for them. However, given the variety of functions ascribed to this region, it is difficult to disentangle influences of cognitive processing, such as attention, and emotional arousal on ACC activation.

**Future Directions**

Future studies may benefit from examination of neural activation following multiple presentations of emotional stimuli. The current study repeated stimuli only once, but habituation is thought to unfold over frequently repeated stimuli and may be more thoroughly studied and understood when pictures are presented more than one time. Additionally, studying
abnormalities in cingulate activity may be better understood in the context of an emotional neural network. The cingulate does not act in isolation in affective processing but is a part of an extended network of prefrontal and subcortical regions which act in concert to generate emotional states and reactions to emotional stimuli and to regulate emotions. Functional connectivity is an approach which examines the temporal correlation between brain regions and may provide more information about how functional abnormalities of the ACC relate to activity in other regions.

In terms of the current findings, it would be interesting to examine whether these abnormalities in ACC activation change following treatment in these disorders, specifically looking at whether heightened ACC activation for neutral stimuli (in BPD) and for unpleasant stimuli (in SPD) normalizes with treatment. Additionally, mediating factors of ACC abnormalities, such as anxiety and depression, warrant further exploration.

Conclusion

BPD and SPD patients both exhibited abnormally high activation of the ACC in the current study. However, the type of picture associated with heightened activation differed between the groups, neutral pictures for BPD and unpleasant pictures for SPD. Furthermore, while SPD patients showed a normalization of this hyper-reactivity, BPD patients did not. The findings in BPD patients suggest a potential social-cognitive deficit characterized by a difficulty in processing neutral stimuli that does not diminish when the stimuli are re-encountered. The SPD findings indicate a hyper-reactivity to unpleasant or aversive stimuli that normalizes when the stimuli are repeated, suggesting that processes to regulate this exaggerated response are intact in this population. Not only do these findings contribute to a better understanding of affective
dysfunction in these individual disorders, it also highlights differences between these disorders and lends support to the diagnostic specificity of the findings.
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