Aggression in Borderline Personality Disorder: A Multidimensional Model

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This article proposes a multidimensional model of aggression in borderline personality disorder (BPD) from the perspective of the biobehavioral dimensions of affective dysregulation, impulsivity, threat hypersensitivity, and empathic functioning. It summarizes data from studies that investigated these biobehavioral dimensions using self-reports, behavioral tasks, neuroimaging, neurochemistry as well as psychophysiology, and identifies the following alterations: (a) affective dysregulation associated with prefrontal-limbic imbalance, enhanced heart rate reactivity, skin conductance, and startle response; (b) impulsivity also associated with prefrontal-limbic imbalance, central serotonergic dysfunction, more electroencephalographic slow wave activity, and reduced P300 amplitude in a 2-tone discrimination task; (c) threat hypersensitivity associated with enhanced perception of anger in ambiguous facial expressions, greater speed and number of reflexive eye movements to angry eyes (shown to be compensated by exogenous oxytocin), enhanced P100 amplitude in response to blends of happy versus angry facial expressions, and prefrontal-limbic imbalance; (d) reduced cognitive empathy associated with reduced activity in the superior temporal sulcus/gyrus and preliminary findings of lower oxytocinergic and higher vasopressinergic activity; and (e) reduced self-other differentiation associated with greater emotional simulation and hyperactivation of the somatosensory cortex. These biobehavioral dimensions can be nicely linked to conceptual terms of the alternative Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) model of BPD, and thus to a multidimensional rather than a traditional categorical approach.

Keywords: alternative DSM-5 model of BPD, borderline personality disorder, neurobiology, personality dimension, reactive aggression

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Aggression can be defined as any behavior directed toward another individual that is carried out with the proximate intent to cause harm (Anderson & Bushman, 2002). The high prevalence of aggression in borderline personality disorder (BPD) is demonstrated by data showing that 73% of individuals diagnosed with BPD have engaged in aggressive behaviors over the course of a year (Newhill, Eack, & Mulvey, 2009), 58% have been “occasionally or often” involved in physical fights, and 25% have used a weapon against others at some point in their lives (Soloff, Meltzer, & Becker, et al., 2003, p. 154). Additionally, individuals with BPD constitute a major proportion of aggression-prone populations such as prison inmates, with prevalence rates of 30% (Black et al., 2007). Studies have found enhanced aggression in BPD compared with healthy and clinical controls irrespective of whether the inclusion was based on categorical Diagnostic and Statistical Manual of Mental Disorders, third edition/fourth edition (DSM–III/IV) diagnosis (e.g., Gardner, Leibenluft, O’Leary, & Cowdry, 1991; McCloskey et al., 2009; Soloff, Kelly, Strotmeyer, Malone, & Mann, 2003) or on dimensional severity scores of BPD traits (e.g., Hines, 2008; Ostrov & Houston, 2008; Raine, 1993; Whisman & Schonbrun, 2009). Therefore, aggression has been regarded as a core feature of BPD (e.g., Siever et al., 2002; Skodol et al., 2002).

Aggression is most widely classified into instrumental and reactive forms (e.g., Berkowitz, 1993). Instrumental aggression refers to planned, goal-directed behavior, whereas reactive aggression is usually triggered by threats, frustration, or provocation and is strongly associated with negative emotions, particularly anger (e.g., Barratt & Felthous, 2003; Poulin & Boivin, 2000). In BPD, aggression is typically of the reactive type (Blair, 2004; Gardner, Archer, & Jackson, 2012; Herpertz et al., 2001). This has also been confirmed by laboratory tests of aggression, in which BPD patients have been repeatedly found to react more aggressively to provocations of a (fictitious) opponent compared with healthy individuals (Dougherty, Bjork, Huckabee, Moeller, & Swann, 1999; McClosey et al., 2009; New et al., 2009). There is broad evidence indicating that aggression in BPD is tightly linked to interpersonal dysfunction, with negative interpersonal events (Herr, Keenan-Miller, Rosenthal, & Feldblum, 2013) and interpersonal problems (Stepp, Smith, Morse, Hallquist, & Pilkonis, 2012) predicting subsequent aggressive behavior in subjects scoring high on BPD traits. Additionally, BPD-associated aggression has been shown to

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primarily emerge in close relationships, with most aggressive acts directed against significant others or acquaintances (Newhill et al., 2009). BPD traits were also linked to intimate partner violence in young to late middle-aged individuals (Holtzworth-Munroe, Meanan, Herron, Rehman, & Stuart, 2000; Ross & Babcock, 2009; Weinstein, Gleason, & Oltmanns, 2012).

**DSM-5** offers two concepts of BPD: In Section II (diagnostic criteria and codes), DSM-5 provides a broad analogy to the categorical polythetic classification of BPD in DSM-IV (American Psychiatric Association, 2013, p. 663). The alternative model of BPD in Section III (emerging measures and models) uses a hybrid approach, which still conceptualizes BPD categorically, but in terms of multiple personality dimensions: All BPD individuals are located on a spectrum of impairments in personality functioning (differentiated into self and interpersonal functioning) and pathological personality traits on the domains of negative affectivity, antagonism, and disinhibition (American Psychiatric Association, 2013, p. 761; see, e.g., Skodol, 2012, for a review).

Our review begins with significant biobehavioral dimensions, meaning fundamental behavioral facets that have been shown to be associated with neurobiological alterations in BPD. The following dimensions have been discussed to underlie aggression in BPD: affective dysregulation, impulsivity, threat hypersensitivity, and empathic functioning. Our approach is to summarize the data related to these biobehavioral dimensions comprising self-reports, behavioral tasks, neuroimaging, neurochemistry, and psychophysiology. We will then provide a working model of aggression in BPD, which illustrates how these biobehavioral dimensions can be nicely linked to conceptual terms of the alternative DSM-5 model of BPD, and thus to a multidimensional rather than a traditional categorical approach. The alternative DSM-5 model could therefore serve as a suitable starting point for future research on aggression in BPD.

**Self-Reports and Behavioral Tasks**

In this section, we will summarize studies that used self-reports and behavioral tasks to investigate the biobehavioral dimensions in the context of aggression in BPD.

**Affective dysregulation** plays a key role in theories of reactive aggression, as they regard reactive aggression to be a result of insufficiently controlled negative affect, predominantly anger (Berkowitz, 2003; Davidson et al., 2000; Siever, 2008). Links between affective dysregulation and aggression in BPD can be seen in studies revealing associations between BPD traits and guilt-, resentment-, and irritation-related self-reported forms of aggression that are described as the “more emotional aggressive” subsdimensions” (Fossati et al., 2004, p. 168). BPD traits also correlated positively with maladaptive forms of emotional coping, such as blaming oneself and venting emotions, which in turn mediated reactive aggression (Gardner, Archer, & Jackson, 2012). Two prospective studies revealed that affective dysregulation fully mediated the relationship between BPD traits and subsequent aggressive behavior in a mixed clinical and community sample (Scott, Stepp, & Pikonis, 2014) and in a solely clinical sample of BPD patients (Newhill, Eack, & Mulvey, 2012). This emphasizes the high relevance of affective dysregulation for aggression in BPD. Affective dysregulation might also predispose the individual to increased experiences of anger or hostility. This was empirically demonstrated by Trull et al. (2008), who used experience sampling methodology (i.e., ambulatory and real-time data collection) to show that BPD patients more frequently experienced extreme spikes of hostility than a clinical control group of depressive patients. The experience of anger may ultimately result in aggressive behavior, as recently illustrated in a study showing that the expression of anger, for example, arguing with other people, predicted subsequent aggressive behaviors in individuals scoring high on BPD traits (Stepp et al., 2012). The relevance of anger for aggression in BPD was also supported by the identification of a subgroup of BPD patients in whom anger proneness and aggression were found to co-occur (Hallquist & Pikonis, 2012).

Reactive aggression has also been considered as a consequence of impulsivity (Coccaro, Sripada, Yanowitch, & Phan, 2011; Gollan, Lee, & Coccaro, 2005; Goodman & New, 2000). Data from BPD patients showed that impulsivity and aggression were positively correlated (e.g., Hollander et al., 2005; Soloff, Meltzer, et al., 2003) and loaded on the same factor in one (Koenigsberg et al., 2001) but not in all studies (Critchfield, Levy, & Clarkin, 2004). Scott et al. (2014) reported that impulsivity did not mediate between BPD traits and aggression. Besides differences in sample characteristics, the latter result might be attributable to the instrument used to assess impulsivity, that is, a composite of different subscales of the NEO Personality Inventory (Costa & McCrae, 1992). As this instrument was designed to assess normative personality traits, it may have failed to capture the aspects of impulsivity specifically related to aggression. Given the strong correlation between impulsivity and anger (García-Forero, Gallardo-Pujol, Maydeu-Olivares, & Andrés-Pueyo, 2009), one might also speculate that the effect of impulsivity on aggression varies as a function of anger. That is, poor impulse control might only (or particularly) result in aggressive behavior under circumstances of momentarily experienced anger.

**Threat hypersensitivity** is a central construct in Blair’s model of reactive aggression (Blair, 2004, 2012). Animal studies indicate that aggressive behavior is displayed when a threat is very close and escape is impossible (Blanchard, Blanchard, Takahashi, & Kelley, 1977). In BPD patients, threat hypersensitivity has mainly been studied by means of facial recognition tasks. Results indicate a biased or enhanced perception of social threat cues in BPD patients (Domes, Schulze, & Herpertz, 2009): Compared with healthy controls, they overreported fear when presented with neutral faces (Wagner & Linehan, 1999), perceived ambiguous blends of facial expression as more angry (Domes et al., 2008), and focused more initial attention (von Csuemern-Lindentjerna et al., 2010a) toward and had difficulties in disengaging from negative facial expressions (von Csuemern-Lindentjerna et al., 2010b). In addition, in a study using eye tracking, BPD patients were found to have more and faster initial reflexive eye movements toward the eyes of very briefly presented angry faces, thus the most threatening and arousing region (Bertsch, Gamer, et al., 2013). These findings suggest that BPD patients misattribute facial emotions, making them susceptible to the experience of threat or provocation, and ultimately to reactive aggression.

1 See Table S1 in the supplemental materials for a detailed description of the cited studies, including sample characteristics, methodology, and key findings.
Threat hypersensitivity may be one of the sources leading to the interpersonal hypersensitivity of BPD individuals. According to the alternative DSM-5 model of BPD, interpersonal hypersensitivity is the “prone[ness] to feel slighted or insulted” (American Psychiatric Association, 2013, p. 766). It has been linked to aggression in BPD by findings showing that criticism or blame predicted aggressive behavior in women scoring high on BPD traits (Herr et al., 2013). Furthermore, fearful forms of attachment that are particularly linked to interpersonal hypersensitivity (Gunderson & Lyons-Ruth, 2008) have been associated with reactive aggression in BPD patients (Critchfield, Levy, Clarkin, & Kernberg, 2008). Threat hypersensitivity might also interact with fundamental assumptions of BPD patients, such as seeing the world and others as dangerous and malevolent, which may lead to feelings of threat and could provoke reactive aggression (Arntz, Dreessen, Schouten, & Weertman, 2004; Arntz, 1994; Pretzer, 1990).

Empathic functioning can be differentiated into cognitive empathy, affective empathy, and supplemental regulatory mechanisms. Analogously to mentalization or theory of mind, cognitive empathy is regarded as the capacity to infer the mental states of others. Affective empathy captures the emotional engagement with other individuals’ emotional displays. The regulatory mechanisms allow the distinction between emotional reactions of the self and the other, hereafter called self-other differentiation (see, e.g., Decety, 2011; Jeung & Herpertz, 2014, for reviews). Impaired empathic functioning is fundamental to the evolution of human aggression (de Waal, 2012; Decety, 2011; Fonagy, 2003). In empirical terms, cognitive empathy in particular has been associated with reactive aggression (Fossati et al., 2009; Jolliffe & Farrington, 2004; Renouf et al., 2010; van Langen et al., 2014). In BPD patients, reduced cognitive empathy was found in studies using self-reports (Harari, Shamay-Tsoory, Ravid, & Levkovitz, 2010; New et al., 2012) or advanced behavioral tasks that approximate real-life social interactions (Dziobek et al., 2011; Preißler, Dziobek, Ritter, Heekeren, & Roepke, 2010; Ritter et al., 2011). The latter tasks—also referred to as ecologically valid tasks—use, for instance, short film clips displaying social interactions, after which participants have to evaluate the intentions, emotions, and thoughts of the interaction partners. Contrary to the finding of reduced cognitive empathy, and despite some inconsistencies (Dziobek et al., 2011), affective empathy seems to be intact in BPD patients (Harari et al., 2010; Mier et al., 2013; New et al., 2012).

First results indicate that BPD patients try excessively to interpret other people’s mental states and/or overattribute the intentions of others, which suggests impairments in self-other differentiation (Sharp et al., 2011). In tasks that can be performed via cognitive or affective empathic involvement, such as the “Reading the Mind in the Eyes task” (Baron-Cohen, Joliffe, Mortimore, & Robertson, 1997), BPD patients outperformed healthy controls (Fertuck et al., 2009; Frick et al., 2012), possibly through (compensatory) over-mobilizing affective empathic strategies, such as emotional simulation (Gallese & Goldman, 1998). In line with the theory of greater emotional simulation in BPD, Matzke et al. (2014) found that compared with healthy controls, BPD patients exhibited higher electromyographic activity of the frowning muscle while viewing negative facial expressions of others such as anger, sadness, and disgust. Exaggerated emotional simulation, however, impacts negatively on the capability of self-other differentiation, resulting in an affect-dominated and unmediated perception of others, known as emotional contagion (Fonagy & Luyten, 2009; Schmahl & Herpertz, 2014). This leaves BPD patients “vulnerable to losing a sense of self” (Fonagy & Luyten, 2009, p. 1362) and to being increasingly overwhelmed by others’ mental states. In the context of dysfunctional intimate relationships, which provoke negative emotions of despair, jealousy (Costa & Babcock, 2008), fear of abandonment (Gunderson, 1996), mistrust, and/or shame (Rüscher et al., 2007), this could result in experiences of anger (Peters, Geiger, Smart, & Baer, 2014), threat, frustration, and eventually reactive aggression.

Interestingly, the pattern of deficient empathic functioning of BPD patients is the opposite of that found in individuals with other aggression-prone personality disorders, such as antisocial or psychopathic individuals. The latter show intact cognitive empathy but impaired affective empathy (Blair, 2013), favoring instrumental forms of aggression (Blair, Peschardt, Budhani, Mitchell, & Pine, 2006) which have been shown not to be abnormally enhanced in BPD (Herpertz et al., 2001). However, studies directly investigating the relationship between empathic functioning and aggression in BPD are still lacking, and further research is needed to disentangle the differential contributions of empathic functioning to aggression in BPD and related disorders.

In the attempt to capture these findings (hereafter related to alterations of the biobehavioral dimensions) within the alternative DSM-5 model of BPD, they can be subsumed under both impairments of personality functioning and pathological personality traits (American Psychiatric Association, 2013, pp. 766–767), and thus the two descriptive levels provided by this classification. Affective dysregulation is closely related to emotional lability, a trait facet of the personality domain negative affectivity. Impulsivity is directly addressed as a trait facet of the personality domain disinhibition. Threat hypersensitivity can be related to both descriptive levels: to the trait facets of emotional lability and hostility on the one hand, and to impairments in interpersonal functioning on the other. Within the latter, it can be attributed to the empathic deficit of BPD patients, namely to interpersonal hypersensitivity and a negatively biased perception of others. The reduced cognitive empathy is encompassed in the description of the empathic deficit of the alternative DSM-5 model. However, reduced self-other differentiation, regarded as a facet of poor empathy in neuroscientific models (Decety & Jackson, 2004), is not directly addressed as an empathic deficit in the alternative DSM-5 model. Instead, it is linked to the “markedly impoverished, poorly developed, or unstable self-image” mentioned as reflecting disturbances of BPD patients’ self-identity.

**Neuroimaging**

Contemporary theories on the neurobiological underpinnings of reactive aggression propose a brain circuitry implicating prefrontal, limbic, and mesencephalic structures. More specifically, in animals, a pathway has been identified that runs from medial amygdala areas to the medial hypothalamus via the stria terminalis, and from there to the dorsal half of the periaqueductal gray. Neurons within the periaqueductal gray matter are activated, causing the autonomic and motor aspects of reactive aggression. Areas modulating the aggressive response include the hippocampus, the cingulate and prefrontal cortices (Blair, 2004; Gregg & Siegel, 2001). In humans, the understanding of the processes leading to
aggression emphasizes the functional relevance of prefrontal and limbic structures. Prefrontal regions, especially the orbital frontal and anterior cingulate cortices, fail to control enhanced affective reactivity of limbic regions such as the amygdala. We will begin this section by describing structural brain abnormalities in BPD patients, and will then summarize results from functional imaging studies.

### Structural Neuroimaging

Structural neuroimaging studies revealed differences in the brain areas mentioned above in BPD patients relative to healthy controls, with smaller amygdala and hippocampal volumes in BPD patients being the most consistent findings across studies (see Nunes et al., 2009, for a meta-analytic review). Less consistent are findings of smaller gray matter volumes in the anterior cingulate (Hazlett et al., 2005; Minzenberg, Fan, New, Tang, & Siever, 2008; Tebartz van Elst et al., 2003) and in orbital frontal cortices (Brunner et al., 2010; Chanen et al., 2008) of BPD patients when compared with healthy controls. Recently, our group reported a larger gray matter volume in the hypothalamus of female BPD patients compared with healthy women (Kuhlmann, Bertsch, Schmidinger, Thomann, & Herpertz, 2013), a structure which is critically implicated in the regulation of aggressive behavior (Hallier, 2013). The hypothalamic volume of BPD patients was positively correlated with scores on the Childhood Trauma Questionnaire (Bernstein & Fink, 1998), suggesting a role of traumatic experiences in volumetric abnormalities of the hypothalamus. In a related vein, Morandotti et al. (2013) demonstrated that gray matter volume loss in the right ventrolateral prefrontal cortex was specifically associated with aggression in those BPD patients with a history of traumatization, indicating a particular impact of traumatization on prefrontal regions and in turn aggression. The relevance of traumatic experiences for aggression is in line with findings of higher aggressive behavior in patients with posttraumatic stress disorder (Van Voorhees et al., 2014). Future studies could therefore benefit from the inclusion of patients with posttraumatic stress disorder as a clinical control group, or a subgroup analysis of BPD patients with and without posttraumatic stress disorder to clarify the contribution of traumatic experiences to aggression in BPD. Kuhlmann et al. (2013) also reported reduced gray matter volume in the cerebellar vermis. Cerebellar structures are connected to the limbic system (Heath & Harper, 1974) and are involved in the regulation of emotional behavior (Scacchetti, Scelfo, & Strata, 2009). Therefore, they might be an additional brain region implicated in affect regulation and aggression.

BPD patients’ aggression has also been reported to be negatively associated with gray matter volume in the hippocampus (Sala et al., 2011; Zetzsche et al., 2007), but not in the amygdala (Zetzsche et al., 2006). Comparing male antisocial offenders with BPD to male antisocial offenders with high psychopathic traits, our group found specific structural abnormalities: Male BPD offenders showed smaller volume in brain regions involved in affect regulation (orbitofrontal and ventromedial prefrontal cortex), whereas psychopathic offenders showed less volume in cortical midline areas (dorsomedial prefrontal cortex and precuneus) that are involved in self-referential emotion processing and self-reflection and could thus mirror psychopathic callousness and poor moral judgment (Bertsch, Grothe, et al., 2013).

Taken together, structural neuroimaging studies revealed abnormalities in gray matter volumes of prefrontal and limbic brain regions in individuals with BPD. These regions are critically implicated in affect dysregulation (Siever, 2008), impulsivity (Coccaro et al., 2011), and threat hypersensitivity (Blair, 2012). Hence, volumetric abnormalities in these regions might be neural correlates of aggressive behavior in BPD.

### Functional Neuroimaging

Consistent with the assumption of prefrontal-limbic imbalance involved in affective dysregulation, functional neuroimaging studies have revealed increased and prolonged amygdala activity in response to (negative) emotional stimuli in BPD patients compared with healthy controls, as well as reduced activity in prefrontal regions involved in regulatory processes such as the anterior cingulate cortex, the medial frontal cortex, the orbitofrontal cortex, and the dorsolateral prefrontal cortex (see, e.g., O’Neill & Frodl, 2012, for a review). In addition, compared with healthy controls, individuals with BPD and comorbid intermittent explosive disorder (BPD-IED) showed impaired functional connectivity between prefrontal and amygdala regions (New et al., 2007).

These brain structures are also implicated in the regulation of impulsivity (Coccaro et al., 2011). In a positron emission tomography (PET) study, significant reductions in fluorodeoxyglucose uptake in the bilateral medial orbitofrontal cortex were found in BPD subjects compared with healthy controls. Covarying for measures of impulsivity rendered the differences between groups insignificant (Soloff, Meltzer, et al., 2003). Recent studies suggest a more complex role of the orbitofrontal cortex in the regulation of impulsivity, with reports of differential abnormalities of its subregions. The resting state blood flow of BPD patients compared with healthy subjects was reduced in medial regions but increased in lateral regions, and was positively associated with trait impulsivity in both regions (Wolf et al., 2012). Assessing aggression and the brain activity of BPD-IED patients during highly provoking situations in a PET scanner, one study found that experimentally induced provocation led not only to increased aggression in the patients, but also to increased glucose uptake in the orbitofrontal cortex and the amygdala compared with healthy controls (New et al., 2009). In addition, compared with healthy controls, BPD-IED individuals failed to activate anterior, medial, and dorsolateral prefrontal regions during high provocation, suggesting a deficit in the mobilization of higher “cognitive control” of aggression. Whereas the orbitofrontal cortex has often been seen as “put[ting] the brakes on” (New et al., 2009, p. 1112) enhanced affective reactivity of limbic regions such as the amygdala, these results render the interplay more complex. This is in line with investigations in healthy controls which revealed enhanced frontal but at the same time reduced orbitofrontal activity during imagined aggression (Pietrini, Guazzelli, Basso, Jaffe, & Grafman, 2000). Thus, activations in the orbitofrontal cortex may be associated with increased or decreased likelihood of aggressive outbursts depending on social cues and context (Blair, 2004). A second analysis of the data used by New et al. (2009) revealed reduced glucose metabolism rates in the striatum of male BPD-IED patients compared with healthy men and might indicate striatal deficits in providing an appropriate situational context to prefrontal inhibitory areas (Perez-Rodriguez et al., 2012).
Prefrontal-limbic imbalance may additionally underlie BPD patients’ threat hypersensitivity, because their exaggerated initial fixation changes toward the eyes of angry faces were related to increased posterior amygdala reactivity to angry facial expressions (Bertsch, Gamer, et al., 2013).

Functional neuroimaging was also used to investigate neural correlates of BPD patients’ deficits in empathic functioning. During tasks assessing cognitive empathy, BPD patients showed reduced activations in the superior temporal sulcus and the superior temporal gyrus compared with healthy controls (Dziobek et al., 2011; Frick et al., 2012; Mier et al., 2013), whereas they showed enhanced activations in the amygdala (Mier et al., 2013) and insula (Dziobek et al., 2011) during affective empathy. One study also revealed a general hypoactivation in the prefrontal cortex and a hyperactivation in the somatosensory cortex of BPD patients compared with healthy controls in a paradigm measuring different facets of empathy (Mier et al., 2013). This suggests that BPD patients have an overactive and poorly controlled amygdala, which might call their unfiltered attention to predominantly negative affective social stimuli. Together with emotional simulation processes reflected in increased activation of the somatosensory cortex, this may lead to emotional contagion, which—as described above—may enhance the likelihood of aggressive reactions.

With regard to the alternative DSM-5 model, the neuroimaging finding of a prefrontal-limbic imbalance in BPD patients underlies the trait facets of emotional lability, impulsivity, and hostility. Hypoactivity of the superior temporal sulcus/gyrus appears to mirror the empathic deficit of BPD patients. Increased activation of the somatosensory cortex can be associated with BPD patients’ tendency to simulate the feelings of others, which may result in what the alternative DSM-5 model conceptualizes as identity disturbance. (American Psychiatric Association, 2013, p. 766).

Neurochemistry

Aggression and related concepts have been linked to a number of neurochemical substances. This section will begin with a summary of physiological and genetic underpinnings of the serotoninergic system, followed by other neurochemical systems and their association with aggression in BPD.

Probably the most consistent neurochemical correlate of aggression is a reduced prefrontal serotonergic concentration and function, which has been regarded as a correlate of impulsivity (e.g., Coccaro & Kavoussi, 1997; Siever & Trestman, 1993; Oquendo & Mann, 2000). So far, investigations showed reduced concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid (CSF) of male BPD patients with comorbid intermittent explosive disorder and/or antisocial personality disorder when compared with clinical controls (Linnoila et al., 1983). 5-Hydroxytryptamine 2a receptor binding abnormalities on platelets were positively associated with aggression in a personality-disordered sample, including BPD patients, but not healthy controls (Coccaro, Kavoussi, Sheline, Berman, & Csernansky, 1997). Pharmacological studies that used serotonergic agonists, such as d-fenfluramine, found a deficit in the central serotonergic functionality in samples solely with BPD patients (Rinne, Westenberg, den Boer, & van den Brink, 2000; Soloff, Kelly, et al., 2003) or in samples with BPD and other personality disorders (Coccaro et al., 1989; Herpertz, Sass, & Favazza, 1997). Male BPD patients had diminished serotonergic synthesis capacity, compared with healthy controls (Leyton et al., 2001). Imaging studies located the central serotonergic deficit of BPD patients mainly in prefrontal brain regions (Leyton et al., 2001; Siever et al., 1999; Soloff, Meltzer, et al., 2003; Soloff, Meltzer, Becker, Greer, & Constantine, 2005; Soloff et al., 2000). Compared with healthy controls, BPD patients were also found to show a reduced serotonin transporter density in the cingulate cortex (Frankle et al., 2005) as well as decreased serotonergic functioning in the hypothalamus (Koch et al., 2007) and in hippocampal regions (Soloff et al., 2007).

Heritability accounts for about 50% of aggression (Rhee & Waldman, 2002) and serotonergic genes; a polymorphism of the serotonin transporter gene (Silva et al., 2007) and a haplotype of the tryptophan hydroxylase gene (Perez-Rodriguez et al., 2010) were associated with aggression in BPD patients. However, the identification of a single gene locus with a major effect size on aggression seems unlikely (Craig & Halton, 2009); rather, gene–environment interactions are expected, such as the enhancement of antisocial behavior in subjects with a polymorphism of monoamine oxidase A (MAOA) when exposed to childhood maltreatment (Byrd & Manuck, 2014; Caspi et al., 2002). BPD gene–environment studies showed that polymorphisms of the brain-derived growth factor (Wagner, Baskaya, Dahmen, Lieb, & Tadić, 2010) and the catechol-O-methyltransferase (Wagner, Baskaya, Anicker, et al., 2010) modulated measures of reactive aggression in BPD patients who had experienced severe life events such as physical or sexual maltreatment. However, because of methodological challenges in gene–environment studies (see, e.g., Carpenter, Tomko, Trull, & Boomsma, 2013), the interpretability of these results is limited.

In addition to the serotonin system, several other neurochemicals might play a role in the relationship between BPD and reactive aggression. Oxytocin has been negatively related to reactive aggression by fostering pro-social behavior and secure attachment patterns (see Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011, for a review). In BPD patients, plasma concentrations of oxytocin were negatively associated with trait aggressiveness (Bertsch, Schmidinger, Neumann, & Herpertz, 2013). First findings suggest a beneficial effect of oxytocin on BPD patients’ threat hypersensitivity, as its intranasal administration reduced the speed and number of reflexive eye movements toward the eyes of angry faces and normalized the hyperactivity of the amygdala for angry compared with happy faces in BPD patients (Bertsch, Gamer, et al., 2013). Oxytocin also modulated neuronal activity in brain areas involved in empathic functioning (Domes, Kumbier, Heinrichs, & Herpertz, 2014)—although this has not yet been shown in BPD patients.

Studies suggest that vasopressin might have contrary effects to oxytocin in the modulation of social behavior (Meyer-Lindenberg et al., 2011) and may increase reactive aggression (Haller, 2013). In line with this, the concentration of vasopressin in the CSF has been associated with aggression in personality-disordered subjects, including BPD patients (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998). Additionally, an interrelation between polymorphisms of the vasopressin receptor gene and reactive aggression in BPD patients has been suggested (Vogel et al., 2012).

Abnormalities in the cortisol system have also been reported in BPD patients, but the results are lacking a clear direction (Zimmerman & Choi-Kain, 2009). Although numerous reports suggest an association between testosterone and aggressive behavior in the general population (Yildirim & Derksen, 2012), findings in BPD...
patients are sparse. One study reported that CSF concentrations of testosterone did not correlate with previous aggressive behaviors in a sample of male patients with various personality disorders, including BPD (Coccaro, Beresford, Minar, Kaskow, & Geracioti, 2007). Recently, a probable deficit in the opioid system has been gaining increased attention in BPD research (Prossin, Love, Koepp, Zubieta, & Silk, 2010), and dopamine may also be a factor in the etiology of reactive aggression (Friedel, 2004; Buchholz et al., 2010). However, to date, studies investigating these substances in aggression of BPD patients are lacking.

Relating these findings to the alternative DSM-5 model, the central serotonin deficit of BPD patients appears to underlie the trait facet of impulsivity, while there are very preliminary data suggesting that high vasopressinergic and low oxytocinergic activity might be related to BPD patients’ empathic deficits.

Psychophysiology

The most robust psychophysiological correlates of aggression in the general population are as follows: (a) low baseline heart rate, which is regarded as an indicator of the underarousal that predisposes individuals toward compensatory stimulation seeking and thus aggression. (b) Enhanced reactivity of heart rate and skin conductance have been linked to aggression, most likely reflecting affective dysregulation. Regarding further psychophysiological parameters, (c) a reduced P300 amplitude in event-related electroencephalographic potentials, although highly dependent on the experimental context, has been associated with impulsivity and aggression, (d) more slow wave activity in resting electroencephalography has also been thought to reflect impulsivity, and (e) an augmented potentiation of the startle eyeblink response to aversive stimuli has been associated with affective dysregulation (Lorber, 2004; Patrick, 2008).

In line with this, BPD patients, when compared with healthy controls, showed an enhanced reactivity of heart rate (Ebner-Priemer et al., 2007) and skin conductance (Barnow et al., 2012), more slow wave activity in resting electroencephalography (Snider & Pitts, 1984), and augmented potentiation of the startle response (Ebner-Priemer et al., 2005; Hazlett et al., 2007). Compared with clinical controls, BPD patients demonstrated diminished P300 amplitude in a 2-tone discrimination task (Blackwood, St Clair, & Kutchera, 1986). The results of a very recent event-related potential study by our group additionally showed enhanced early visual potentials (occipital P100) in BPD patients compared with healthy controls in a facial recognition task with blends of happy versus angry expressions (Izumiya, Nagy, Mancke, Herpertz, & Bertsch, 2014), indicating an involvement of very early visual processes in threat hypersensitivity.

With regard to the alternative DSM-5 model of BPD, psychophysiological data most notably reflect the trait facets of emotional lability (enhanced skin conductance, heart rate reactivity and augmented startle response) and impulsivity (increased slow wave activity and reduced P300 amplitude). Enhanced P100 amplitudes probably point to early attentional hypervigilance to threat-related social cues, favoring hostility. These studies, however, have rarely included measures of aggression, making implications for the manifestation of aggressive behaviors in BPD premature.

Multidimensional Model of Aggression in BPD

In this concluding section, we will use the reviewed data to propose a multidimensional model of aggression in BPD. We summarize findings of aggression in BPD from the perspective of the biobehavioral dimensions affective dysregulation, impulsivity, threat hypersensitivity, and empathic functioning; and then link these findings to the alternative DSM-5 model of BPD (see also Figure 1).

Based on this approach, affective dysregulation, which has been shown to be associated with prefrontal-limbic imbalance, enhanced reactivity of heart rate, skin conductance, and startle response, is close to the trait facet of emotional lability in the alternative DSM-5 model. Impulsivity is also associated with prefrontal-limbic imbalance as well as central serotonergic dysfunction, more electroencephalographic slow wave activity and reduced P300 amplitude in a 2-tone discrimination task, and is directly addressed as a trait facet in DSM-5. The biobehavioral dimension of threat hypersensitivity reflected in enhanced perception of anger in ambiguous facial expressions, greater speed and number of reflexive eye movements to angry eyes, prefrontal-limbic imbalance, and enhanced P100 amplitude in response to blends of happy versus angry facial expressions can be linked to the DSM-5 trait facets of emotional lability and hostility. Additionally, threat hypersensitivity is related to impairments in interpersonal functioning, more specifically to interpersonal hypersensitivity and a negatively biased perception of others, which might be modulated by oxytocin. Reduced cognitive empathy was shown to be associated with hypovasopressin in the superior temporal sulcus gyrus and is encompassed in the description of the empathic deficit of DSM-5. Preliminary data suggest an additional role for lower oxytocinergic and higher vasopressinergic activity in reduced cognitive empathy. Finally, reduced self–other differentiation coupled with greater emotional simulation and hyperactivation of the somatosensory cortex might contribute to BPD patients’ identity disturbance. Notably, these various biobehavioral dimensions may contribute to aggression to different extents within the individual BPD patient.

Importantly, we suppose that the biobehavioral dimensions are highly interconnected. This is demonstrated by several findings. The serotonergic dysfunction is related not only to impulsivity but also to affective dysregulation (Canli & Lesch, 2007; Davidson et al., 2000), and the brain regions implicated in affective dysregulation are also linked to impulsivity (Goodman & New, 2000), empathic functioning (Adolphs, 2009) and threat hypersensitivity (Blair, 2012). Affective dysregulation mediates the emergence not only of threat hypersensitivity (Gratz, Dixon-Gordon, Breetz, & Tull, 2013) but also of deficits in empathic functioning (Sharp et al., 2011). Finally, within the framework of the alternative DSM-5 model of BPD, hostility is a trait facet that has been subsumed under both pathological personality domains, antagonism and negative affectivity (American Psychiatric Association, 2013, p. 780).

Limitations

Interestingly, the biobehavioral dimensions shown to underlie aggression in BPD can be nicely related to the terminology and definitions of the alternative DSM-5 model of BPD according to Section III. However, some inconsistencies have to be discussed. In the alternative DSM-5 model, interpersonal hypersensitivity is related to the empathic deficit, whereas reduced self–other differentiation, a facet of empathy in concepts of neuroscience (Decety & Jackson, 2004), is subsumed under the identity disturbance. Although this primarily
seems reasonable to us, interpersonal hypersensitivity also encompasses aspects that are only partially embraced by the concept of empathy in DSM-5, but also overlaps with descriptions of trait facets, for example, by partially overlapping with hostility, and closely interacting with emotional lability and impulsivity in the context of escalating transactional processes. Consequently, the conceptual boundaries between the impaired personality functioning and the pathological personality traits are not clear-cut and are most likely to be intertwined, as already discussed by Livesley (2012) and, thus, need to be further developed and conceptually sharpened in the future.

However, the dimensional approach of the alternative DSM-5 model seems to explain the complex multifaceted behavioral construct of aggression better than a categorical approach to BPD, which has raised questions such as whether aggression is, in fact,
an inherent characteristic of the disorder, or a subtype of BPD (Hallquist & Pilkonis, 2012; Kernberg & Caligor, 2005), or rather a co-occurring phenomenon related to comorbid personality pathology, such as antisocial personality disorder or psychopathy (Allen & Links, 2012). The latter assumption seemed to be confirmed by the nonsignificant relationship between aggression and BPD after statistical controlling for Axis I or other comorbid Cluster B personality disorders (Berman, Fallon, & Cocco, 1998; Haller & Miles, 2003; Johnson et al., 2000). However, because almost two thirds (66%) of BPD patients who do not fulfill the criteria for antisocial personality disorder still engage in aggression (Newhill et al., 2009), aggression is more likely to be linked to BPD psychopathology itself, and further investigations of (neuro)biological and psychological correlates of reactive aggression in patients with BPD are highly important.

The specificity of some of the data presented above requires further exploration. For instance, associations between prefrontal dysfunction and aggression have been reported in a variety of psychiatric conditions (Bassarath, 2001; Brower & Price, 2001) and the same holds true for alterations in the serotonin system (Bortolato et al., 2013), again questioning a purely categorical approach.

It should be considered that the range of effect sizes in the above-presented data is immense: from as little as 5% shared variance for BPD traits and reactive aggression (Gardner et al., 2012) to >57% mediation of aggression by interpersonal problems in individuals with BPD traits (Stepp et al., 2012).

Finally, the aim of this article was not to completely recontextualize the relationship between aggression and BPD or to comprehensively review all available data. We rather intended to provide a specific framework for aggression in BPD that poses unanswered questions and stimulates further discussion and integrative research.

Outlook

Pathological forms of aggression are an individual as well as a societal burden that remain far from being understood (World Health Organization, 2007). With regard to aggression in BPD, a number of questions need to be addressed in future research.

First, the construct validity, that is the accuracy of the existing paradigms for the study of reactive aggression in BPD (Giancola & Chermack, 1998, p. 238), has been questioned. The restriction to stimulus–response sequences as conducted in most of the experimental paradigms leaves out underlying motives and intentions of stimulus–response sequences as conducted in most of the experimental paradigms leaves out underlying motives and intentions of aggressive behavior (Tedeschi & Quigley, 2000) and the relationship between provocateur and aggressor that seems to be of particular importance in BPD. Thus, instruments that mimic aggressive behavior. First results in this regard are promising, especially for dialectical behavioral therapy (Evershed et al., 2003; Frazier & Vela, 2014; Nelson-Gray et al., 2006; Shelton, Kesten, Zhang, & Trestman, 2011). In terms of biological treatments, the search for and investigation of new agents, for instance oxytocin agonists or vasopressin antagonists, could be promising.

In conclusion, the investigation and classification of aggression in BPD requires a multidimensional approach. In our opinion, the alternative DSM-5 model can be used as a framework to conceptualize BPD-associated aggression and its underlying biobehavioral alterations. Further research pursuing a multimethod approach on the behavioral and the pathophysiological level is needed to explicate the fundamental biobehavioral dimensions in the field of personality disorders. Analogously to research in the major mental disorders (Insel, 2014), these dimensions are significant for the understanding of etiology and pathophysiology of BPD, and should facilitate the development of new treatments for those affected.

References


AGGRESSION IN BPD: A MULTIDIMENSIONAL MODEL


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