A New Look at Borderline Personality Disorder and Related Disorders: Hyper-Reactivity in the Limbic System and Lower Centers

Michael H. Stone

Abstract: Borderline Personality Disorder (BPD) has been often described recently as a condition characterized by emotional dysregulation. Several other conditions share this attribute; namely, Bipolar Disorder (BD), Attention-Deficit/Hyperactivity Disorder (ADHD), Intermittent Explosive Disorder (IED), and Major Depressive Disorder (MDD). The dysregulation is not always in the same direction: BPD, BD, ADHD, and IED, for example, show over-reactivity or "hyperactivity" of emotional responses, whereas patients with MDD show emotional sluggishness and underactivity. At the clinical/descriptive level the "over-reactive" conditions appear separate and distinct.

BPD constitutes a large domain within the psychopathological arena, appearing to contain within it a variety of etiologically diverse subtypes. Among the latter is a type of BPD linked closely with Bipolar Disorder; family studies of either condition show an overrepresentation of both: BPD patients with bipolar relatives; Bipolar patients with BPD relatives. A significant percentage of children with ADHD go on to develop either BPD or BD as they approach adulthood. If one shifts the spotlight to neurophysiology, as captured by MRI studies, however, it emerges that an important subtype of BPD, and also BD, ADHD, and IED—share common features of abnormalities and peculiarities in the limbic system and in the cortex, especially the prefrontal cortex. Deeper subcortical regions such as the periaqueductal gray may also be implicated in strong emotional reactions. The diversity of clinical "over-reactive" conditions appear to harken back to a kind of unity at the brain-change level. There are therapeutic implications here, such as the advisability of mood stabilizers in many cases of BPD, not just for Bipolar Disorder.

Michael H. Stone, M.D., Professor of Clinical Psychiatry, Columbia College of Physicians & Surgeons.

Psychodynamic Psychiatry, 41(3) 437–466, 2013

Borderline Personality Disorder (BPD) enjoys two curious distinctions. In the domain of personality disorder, BPD is the disorder to which the most voluminous literature is devoted. What makes this ironic is that its defining characteristics, as outlined in the *DSM-IV*, do not include any personality *traits* as the latter are ordinarily understood, with the possible exception of irascibility. That word is not actually used, but is implicit in the item called "inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, controlling anger, recurrent physical fights" (American Psychiatric Association, 1994, p. 654). Since a minimum of only five of the nine items are needed to establish BPD as a diagnosis, this allows for many combinations where irascibility is not among them. In everyday practice, however, the "typical" BPD patient will show impulsivity, self-damaging acts (including suicidal behaviors), inordinate anger, and lability of mood. The latter is defined further as "marked reactivity of mood," as exemplified by intense episodic dysphoria, irritability, or anxiety. These point to both depressive (dysphoria) and, to a lesser extent, manic (irritability) alterations of mood. Irritability is of course not limited to persons of a manic predisposition, so the connection between "mood lability" and Bipolar Disorder (BD), while hinted at, is not that strong. But for the most part, the features of BPD point to a kind of characterologic excess: a tendency to over-react to various stimuli, especially within the interpersonal field.

Over-reactivity is noted in a number of other disorders; namely, bipolar disorder, attention-deficit disorder with hyper-reactivity (ADD/H), intermittent explosive disorder, as well as in certain cases of antisocial personality in which short-temperedness is a dominant feature. Apart from the "red-thread" of over-reactivity that appears to run through this collection of disorders (to which childhood conduct disorder, and some cases of psychosis and drug-induced states could be added), the disorders themselves are differentiated, solely by characteristics at the descriptive or clinical level. Particularly in the domain of personality disorder, *DSM* has maintained an "atheoretic" stance, avoiding the tendency to anchor the various disorders to their underlying etiological roots. This was a prudent choice at the time, given that what was known about causative factors was either insufficiently determined from a scientific standpoint, or else too ambiguous to permit any one-to-one correlation between condition and cause.

If we are to come closer to discovering links between BPD and antecedent factors that merit significance as causes, in contrast to mere correlations, it is more than ever an urgent matter to put under the

microscope the whole array of conditions and syndromes that can be placed under the heading of BPD. BPD is not unitary even at the clinical/descriptive level; it is not to be expected there would be a single underlying causative factor, anymore than there would be for congestive failure or hematuria. Recently, Schmahl, McGlashan, and Bremmer (2002) have argued that BPD, rather than being thought of as a specific disorder, is better conceptualized via an amalgam of dimensions, each with a possibly different biological profile and different clinical pictures in different patients. They suggested attention to such dimensions as interpersonal stress, impulsivity, dissociation, and self-injurious behavior. They further suggested that genetic and environmental factors commingle in different BPD patients—to bring about brain alterations that then nudge emerging symptomatology along these different paths, impulsivity becoming the major variable in one patient, self-injury in another, affective instability in still others, and so on.

Commenting on personality disorders in general, Depue and Fu (2012) showed how meta-analysis of personality disorders in general manifested higher levels of *neuroticism* and lower levels of social closeness (or "*agreeableness*"), within the context of the Five Factor Model of Widiger and Costa (2013). As a consequence, they argued that "most individuals with personality disorders are subject to *negative emotionality, heightened stress-reactivity*, and *impaired interpersonal behavior*" (emphasis mine, p. 167). The supposedly discrete categories of personality, as outlined in *DSM* for example, can better be understood as different colorations—different patinas, if you will—covering the surface of an underlying condition whose basic elements are those same three qualities emphasized by Depue and Fu. As for the element of "impaired interpersonal behavior," I believe one can build a case that *narcissism* (or self-centeredness) is common to almost all the categories of personality disorder (think of the schizoid's aloofness, the paranoid's reluctance to confide in others, the antisocial's disregard for the safety of others, the stormy relationships of the borderline, the stubbornness and miserliness of the obsessive, and so on). What we call "narcissistic PD" represents a personality type in which the self-centeredness is simply more striking and rises to a greater height in intensity—than what is observable in the other PDs. It is for reasons of this sort that Depue and Fu maintain that "personality disorders as distinct entities do not exist" but instead represent "emergent phenotypes that arise from the interaction of extreme values on critical subsets of major personality traits" (p. 167).

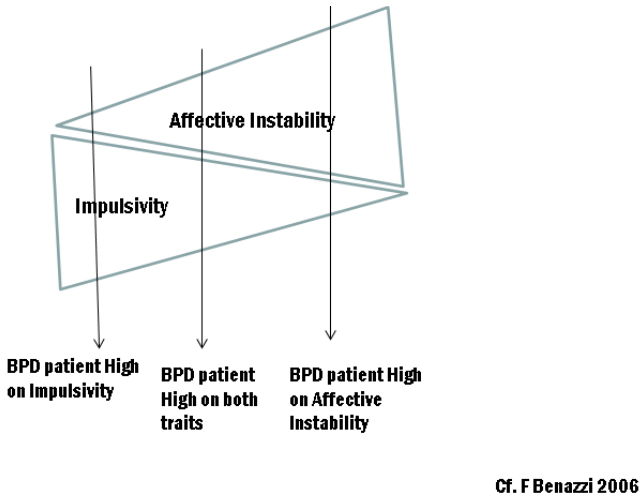


FIGURE 1.

BPD AND BIPOLAR DISORDER

The relationship between BPD and bipolar disorder has been the topic of a lively controversy for several decades (Magill, 2004). Some have taken the position that BPD, in many instances at least, is either a close cousin or else actually a variant of bipolar disorder (Akiskal, 1981; Stone, 1981). Others have argued against this, contending that the two are not necessarily so closely related, though granting that in isolated cases the two conditions do coexist (Gunderson, 2001). In this regard Gunderson in his perceptive analysis of existing data provided a table showing the overlap of BPD and bipolar disorder: if one began with BPD, then 15% of the patients also had a bipolar disorder (10% with Bipolar II; 5% with Bipolar I). But if one first looked at patients with bipolar disorders, then 35% were "comorbid" for BPD (20% of the Bipolar IIs; 15% of the Bipolar Is). Overlap rates (with bipolar and also with other conditions such as eating disorders and substance abuse) tended to be higher, if one began with hospitalized BPD patients, as one might expect (Gunderson, 2001, pp. 38-39).

Recently, in a large-scale study of patients with a major depressive episode (MDE), Perugi, Angst, et al. (2013) have shown that almost one in ten patients with MDE could also be diagnosed with BPD; furthermore, bipolar disorder was significantly more common in the BPD subgroup than in the MDE patients who did *not* show BPD. In an effort to tease out which BPD items might correlate better with bipolar

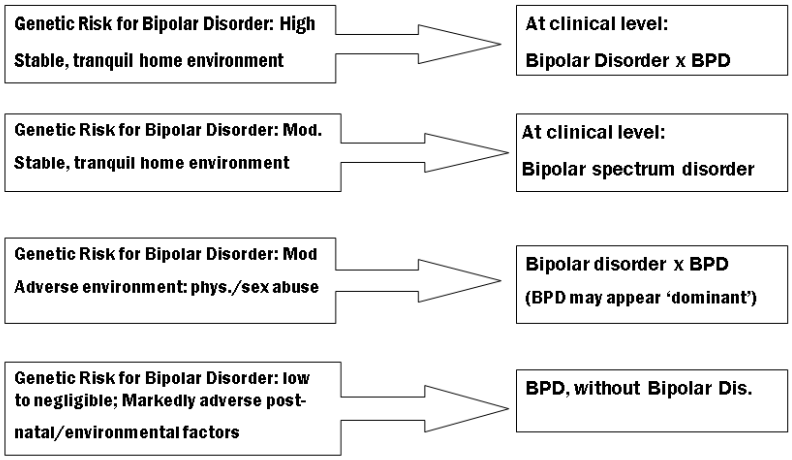


FIGURE 2.

type II disorder (BP-II), Franco Benazzi (2006) noted that the nine BPD descriptors could be bifurcated into two major groups: those related to "*affective instability*" (including unstable mood, unstable relationships, unstable self-image, emptiness, and anger) versus those related to "*impulsivity*" (impulsivity itself, along with self-damaging acts, abandonment avoidance, and paranoid ideation). *Affective instability* emerged in this study as more closely related to BP-II, whereas *impulsivity* did not correlate with BP-II. To the extent that hypomania is considered a core feature of BP-II, however, Benazzi (2008) found that hypomania was not a common symptom in BPD. In regard to suicidality, known to be a high risk factor in borderline patients (Stone, 1990), the presence of bipolar II comorbidity and impulsivity in a sample of BPD patients was more strongly associated with suicidality than was the case with BPD patients in whom impulsivity was not a feature, but who did show affective instability (Rihmer & Benazzi, 2010). Some of the controversy concerning BPD "versus" bipolar disorder hinges on the diagnostic habits of various researchers. As "affective instability" of BPD, for example, increases in intensity, it eventually crosses a boundary line (yet another kind of "borderline"!) and passes over into the "rapid cycling" of bipolar disorder. In bipolar-spectrum disorders there is often rapid switching from euphoria (or highly irritable states) to depression. Mackinnon and Pies (2006) make the point that there is a biological overlap between these two clinical conditions in many cases, making of BPD versus bipolar in such cases—a distinction without a difference.

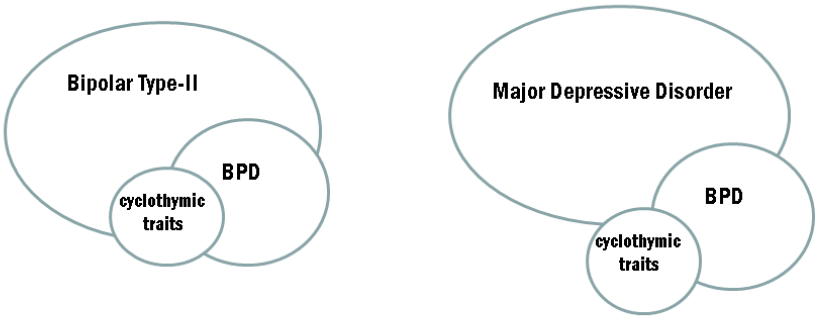


FIGURE 3.

The multiple variations in affective instability and impulsivity among series of BPD patients can be pictorialized as in Figure 1.

Much of the controversy concerning these two disorders, seemingly different at the descriptive/clinical level, can be resolved when we take into consideration how diverse BPD is—if one focuses only on the descriptive level. As I suggested recently (Stone, 2012), there are literally thousands of varieties of BPD once one takes into consideration not only the "polythetic" definition (allowing for over 250 varieties manifesting 5 or more of the 9 criteria), but also the admixture of BPD with other personality categories of *DSM* (since BPD never occurs without some traits of at least one other disorder) and with other symptom-conditions of the sort depicted in Axis I of *DSM-IV* (viz. eating disorders, anxiety disorders, dissociative disorders, mood disorders . . .). The final tally is in the thousands of different subtypes within the broad domain of BPD. Thanks to this heterogeneity, it is understandable how certain investigators have concluded that BPD and bipolar disorder are separate conditions, given that the percentage of overlap seems quite modest in many studies. But if one views BPD as a huge *omnium gatherum* of outwardly similar clinical conditions, it is only to be expected that concomitant bipolar disorder represents only a "small fraction" of all the BPD cases (such as the 9.3% in Perugi et al.'s study). Hence the conditions, viewed from this perspective, appear "separate." If, in contrast, one is willing to step down from the descriptive level to the biological level, it becomes reasonable to suppose that within the broad territory of BPD (seen as an endophenotype—a "plaza" into which many etiological avenues converge), there exists a smaller region in which bipolar disorder, with its genetic underpinning, is the primary condition; BPD, an accompanying epiphenomenon brought about either because of the

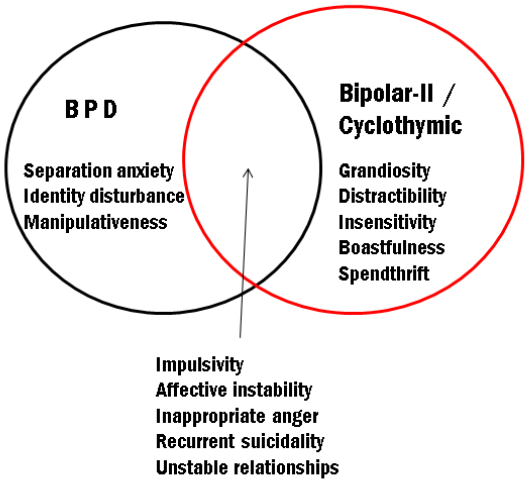


FIGURE 4.

severity of the genetic disorder itself, or because of adverse environmental conditions that become superimposed on an even less severe genetic predisposition—the two together combining to create a *Bipolar* × *BPD* clinical condition at the outward, phenomenological level. Some of the scenarios in which the combined picture of bipolar disorder and BPD could arise are depicted in Figure 2.

If we look at the whole domain of bipolar disorders, we can make the case that there is a fair degree of overlap with BPD and also with one of the temperaments Kraepelin once described as associated with "manic depression" (as bipolar disorders are now more often called); namely, "cyclothymic." A lesser degree of overlap exists even in persons who first come to clinical attention with a "major depressive episode" (as noted in Perugi, Angst, et al., 2013). Figure 3 shows the approximate degree of overlap among these conditions.

If, in contrast, we look at the domain of BPD from the standpoint of the various clinical features, a fair degree of overlap exists with the features of bipolar disorders (especially with those of Bipolar II). Table 1 shows the comparison of the two conditions, with respect to a dozen characteristics. Some are mainly associated with bipolar disorders (desultory thought, diminished need for sleep, and pressured speech); others are more closely associated with BPD (early sexual abuse, self-damaging acts). Some of the overlapping and dissimilar traits are also

Table 1.

BPD	Bipolar Disorder
Aggressivity ++	Affective Lability ++
Desultory Thought	Aggressivity ++
Diminished Need for Sleep	Desultory Thought ++
Affective Lability ++	Diminished Need for Sleep ++
Early Sexual Abuse ++	Early Sexual Abuse +
Explosive Temper ++	Explosive Temper ++
Family History of Mood Dis. ++	Family History of Mood Dis. +++
Heightened Sex Drive +	Heightened Sex Drive ++
Impulsivity +++	Impulsivity +++
Irritability/Anger Proneness +++	Irritability/Anger Proneness ++
Rapid Pressured Speech	Rapid Pressured Speech ++
Self-Damaging Acts +++	Self-Damaging Acts +

Note. The number of "+" symbols associated with each clinical feature indicates whether the feature is either slightly (+), moderately (++), or markedly (+++) associated with the corresponding diagnosis. Lack of "+" means that the feature is not associated with the condition.

depicted in the Venn diagram in Figure 4 (adapted and modified from Gunderson, 2001, p. 42).

Whether one's primary clinical experience is with BPD or instead with bipolar disorders, a fair number of patients will be seen—in whom the features of both conditions coexist in abundance. It is such "comorbid" patients who tempt us to search for what might be common elements at a different level of discourse: the biological layer, or what some have called the "neurobehavioral" level (Depue & Fu, 2012) or "neurophysiological" level (Panksepp & Biven, 2012). If important similarities can be ascertained at this level, this would point the way to a common origin—pertaining to underlying alterations of a similar nature in the brain—to what otherwise at the more external level of clinical experience appears as "different" conditions.

SOME NEUROPHYSIOLOGICAL ASPECTS OF BPD

A number of recent studies, based on functional magnetic resonance imaging (fMRI) in borderline patients, have highlighted abnormalities in brain function that correlate well with the clinical observations of impulsivity, inhibitory dyscontrol, and over-reactivity—abnormalities that, taken together, are key features of borderline psychopathology. Within the limbic system, the amygdala is an important center for the

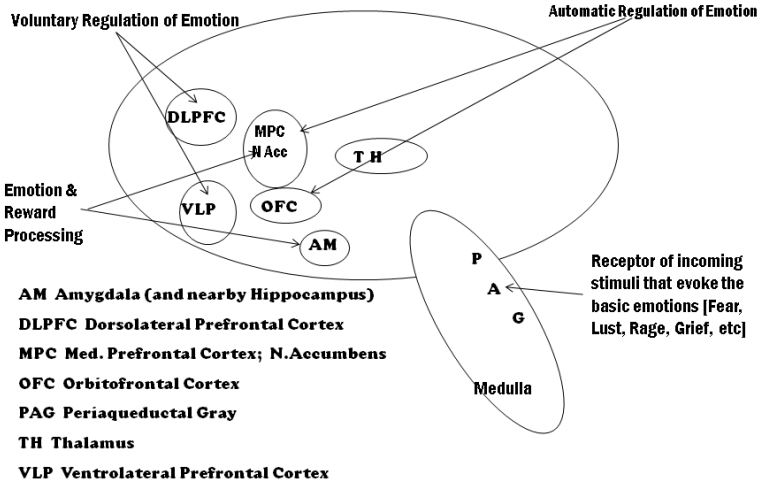


FIGURE 5.

processing of emotions, particularly those of fear, rage, and lust (Panksepp & Biven, 2012, p. 228). In a meta-analysis of 11 studies of borderline patients, Ruocco, Amirthavasagam, and Zakzanis (2012) found volume reduction in the amygdala, but also in the hippocampus (of which one function is to transmit contextual information to the amygdala—such as the setting where a frightening experience took place; Rodrigues et al., 2011). Others have emphasized the role of severe early stress in exerting a damaging effect on the brain, especially in the hippocampus—suggesting stress as a significant factor in the neurobiology of BPD (Wingenfeld, Spitzer, Rullkötter, & Löwe, 2010). Weninger, Lange, Sachsse, and Irle (2009) take this a step further, noting that patients with BPD and PTSD showed marked reduction in amygdala size (34%) and a smaller reduction in hippocampus size (21%). Even BPD patients exposed to trauma, but who did not develop the PTSD picture, showed amygdala reduction (22%).

The emotional dysregulation characteristic of BPD generally involves reactions to stressful (for the most part, interpersonal) situations that are exaggerated in intensity and expressed too quickly and without proper forethought—hence the *DSM* items of stormy relationships and inordinate anger. But this dysregulation is associated with such neurobiological abnormalities (besides those of the amygdala and hippocampus) as lower activation of the dorsolateral prefrontal cortex and higher activation in the cingulate cortex (Radaelli et al., 2012). These changes

were more marked in patients with a combination of *mood disorder* and BPD (as opposed to those without BPD). Irle, Lange, Weninger, and Sachsse (2005), meanwhile, noted in their MRI study a reduced size in the parietal lobe of borderline patients—especially in the superior (precuneus and post-central gyrus) and inferior parietal cortices of patients who had endured severe physical and sexual abuse as children. In those patients with dissociative symptoms and depersonalization, however, they noted an increase in precuneus size. As for the dorsolateral prefrontal cortex (DLPFC), this region is involved in working memory and in the monitoring and adjustment of behavior. Impairment of the DLPFC may interfere with its functions of planning and selecting the most prudent response to new (and challenging) stimuli, and of repressing unwanted memories. Bouchard and colleagues (Bouchard, Lemelin, Dubé, & Giguère, 2010) also champion the idea of underlying brain changes that contribute importantly to the development of what later gets labeled "borderline." They mention that the executive and frontal lobe dysregulation associated with the cognitive defects in BPD may stem from inborn frontal lobe cognitive deficits (such as may relate to bipolar disorder) or to the neurophysiological sequelae of adverse factors in childhood—especially sexual abuse. One impact of *early sexual abuse* may be the induction of epigenetic changes—in which (postnatal) experience can alter gene expression, leading to the development or intensification of certain personality attributes (Panksepp & Biven, 2012, p. 240; Riggs, Russo, & Martiensse, 1996). Results may include heightened mood disturbances, mistrustfulness, changes in the sexual sphere (promiscuity or else avoidance of sex), and irascibility—all of which figure in the histories of various borderline patients. Exaggerated reactions of this sort may be triggered by a hyper-responsiveness of the amygdala—brought about partly by *diminished inhibition* from the medical prefrontal cortex.

The prefrontal cortex as a whole is often referred to in connection with inhibitory control—essentially, the brain's "braking system." But different regions appear to mediate different specific functions. The *dorsolateral prefrontal cortex* (DLPFC), mentioned above, monitors and adjusts behavior, besides being involved in working memory. The *ventrolateral prefrontal cortex* (VLPFC) selects, in conjunction with the amygdala, a response to threats (as in incoming stimuli that provoke anxiety). The orbitofrontal cortex (OFC) is the highest integration center for emotional processing, involving the appreciation of the emotions of self and others, thinking about the feelings of others ("mentalization"), and inhibition of inappropriate behaviors. Dysfunction in the OFC can lead to antisocial or hypomanic traits as well as to inappropriate sexual behaviors—and may figure in the psychopathology of BPD,

bipolar disorder, and ADD/H, that is to say: "over-reactive" states in general. The *ventromedial prefrontal cortex* (VMPFC), in connection with the anterior cingulate gyrus, amygdala, insula and nucleus accumbens, subserves the valence and emotional tone of stimuli and figures in the experience of empathy. Figure 5 shows a number of these subdivisions of the frontal cortex "higher centers."

Minzenberg, Fan, New, Tang, and Siever (2007), in addition to underscoring the impact of fronto-limbic activity in BPD (viz., hyper-reactivity in the amygdala and greater deactivation in the anterior cingulate to fear-inducing situations), suggest that the avoidance of attachment in some BPD patients may develop over time—as a compensation for the emotional consequences of frontal-executive dysregulation. In an earlier article I had alluded to this paradoxical tendency in certain BPD patients (who generally tend to be overly hungry for attachment to a significant other) to give up, after some years of "stormy" relationships—opting for a more reclusive life (Stone, 1988). BPD patients of this sort eventually remove themselves from the interpersonal field (especially where intimacy is involved) in which their tendency to rage outbursts, fits of jealousy, and other manifestations of limbic over-reactivity were formerly ignited.

POOR INHIBITORY CONTROL: A CLOSER LOOK

The impulsivity, inordinate anger, self-damaging acts, and stormy relationships that, when all present, move us to categorize a patient as "borderline," have in common the characteristics of a brain given to reactions that are too rapid, too intense, and insufficiently modulated by the "higher centers" in the neocortex. In simpler language, the "bottom-up" centers, where incoming stimuli first exert their impact, are not subject to sufficient "braking" by the "top-down" neocortical (especially, frontal lobe) centers. The inhibitory control that the top-down centers are supposed to exert is quite below par, and in more extreme situations, appears to fail altogether. Using the computer as an analogy, it is as though the higher centers are suddenly shunted "off-line."

Apart from volumetric changes in the neocortex and limbic system, differences in neurotransmitter availability have also been implicated in the compromised top-down control (New, Goodman, Triebwasser, & Siever, 2008). Siever (2008) draws attention to insufficient serotonergic facilitation of top-down control, along with excessive catecholaminergic stimulation, and—in the subcortical regions—imbalances in the glutamate (stimulating) and GABA (inhibitory) systems. These

combined abnormalities appear to play a role in the hampered prefrontal braking system and in the amygdalar hyperactivity (e.g., to fear-inducing stimuli, perceived threats, and the like) that contribute to the heightened anger and aggression in a variety of psychiatric disorders, of which BPD and bipolar disorder are examples. Many manic patients, for example, walk a fine line between euphoria, and an irritability that may rise to outbursts of aggressive behavior. In a proportion of bipolar persons, childhood ADD/H appeared as a prelude to the future manic condition. The outcome at the clinical/descriptive level of these genetic and neurobiological abnormalities often depends, nevertheless, upon the presence or absence of early abuse (where combinations of verbal, physical, and sexual abuse, and also parental neglect all figure in the equation). Pally (2002) speaks, in this regard, of the synergy of nature and nurture that may play a determinative role in whether a person with (moderate) bipolar genetic risk remains simply as bipolar, or whether adverse environmental factors lead to the clinical picture of BPD.

A clinical vignette may serve as an illustration:

> A businessman in his mid-40s had a long history of bipolar illness, the manic episodes much more common than the depressive. His temperament was "manic" (as described by Kraepelin: cf. Stone, 1980, p. 326), and included such qualities as heightened self-confidence and cheerfulness, hasty judgment, raucous laughter, sexual promiscuity, alcoholism, compulsive joking, overspending, and irascibility. He was in the midst of an on-again/off-again affair with a much younger, tempestuous and hot-tempered woman whom another doctor had diagnosed as "borderline" primarily because of her suicide gestures and wild behavior. Passionate sex would be followed by high-volume arguments, after which they would break "forever" up but then come together again a few days later. During the "break-up" periods, he would pick another woman in a bar and have a "one-night stand" in his apartment. But the next day, after the two lovers reunited, she would find a champagne-cork in his basket, and then create an angry, high-decibel scene sparked by his "betrayal," followed by some destructive behavior, such as "keying" his car (i.e., scratching the outside of his car with a key). He would retaliate by tossing her clothes out his apartment window. One time, after another break-up, he was distraught, got drunk, called me to demand a session right away and came to the lobby of my building. Unable to provide that, I offered a time the next morning. But the doorman in my building informed me that he had stormed out of the building—but only after urinating into the flower pot in the entrance-way. Both parties in this romantic relationship, one bipolar, the other borderline, showed inhibitory dyscontrol to the point of caricature. The young woman had been molested sexually by her father, which contributed to her distrust of men, to her jealousy, and to her aggressivity. The businessman, having been raised in a strict but non-abusive family,

apparently came by his manic temperament and bipolarity via risk genes for bipolar disorder.

As for the role of the amygdala, it has become customary to assign this limbic-system organelle pride of place in the mediation of emotion, particularly the emotion of fear—both in our experience of fear and in our recognition of fear (via facial expression, for instance) in other people. As we have noted, many authors underline the importance of the amygdala, along with the prefrontal cortical regions, in their hypotheses regarding inhibitory dyscontrol not only in BPD but in other "dramatic cluster" personality disorders, viz., antisocial and histrionic (cf. Siever & Weinstein, 2009). Coccaro and colleagues (Coccaro, McCloskey, Fitzgerald, & Phan, 2007) underlined their significance for impulsive aggression, and also reactive aggression, not only in BPD and in antisocial personality, but also in intermittent explosive disorder (Coccaro et al., 2007; Coccaro, Sripada, Yanowitch, & Phan, 2011). The link between abnormal fronto-limbic circuitry and behavioral dyscontrol is not limited to fear, but is pertinent to negative emotion in general (Brendel, Dtern, & Silbersweig, 2005). As exemplified by the clinical vignette above, impulsive and emotionally dysregulated behaviors in patients with BPD occur predominantly in an interpersonal context (Hughes, Crowell, Uyeiji, & Coan, 2012). Besides *fear* and *rage*, the emotion of *sadness* was also handled in suboptimal ways when induced in a sample of borderline patients. This was felt to reflect a greater reduction in the activation of the endogenous opioid (specifically, in the mu-opioid receptors) in the patients than in the control group (Prossin, Love, Keoppe, Zubieta, & Silk, 2010). The importance of the mu-opioid system in BPD was also underlined in a recent study by Stanley and Siever (2010).

The above-mentioned triad of fundamental negative emotions, *fear, rage*, and *sadness,* happen to correspond to three of the seven basic emotions common to mammals (including ourselves), as outlined by Panksepp and Biven (2012). The basic seven are: Seeking, Care, Fear, Rage, Lust, Joyful Play, and Panic/Grief (the latter also underlies the related emotion of *sadness*). Curiously enough, Panksepp's schema maps perfectly with the list of basic emotions elaborated by Descartes (1650; Stone, 1979), namely: *Admiration* (equivalent to Seeking—curiosity, having a strong interest in certain people or things), *Love* (similar to Care), *Hate* (similar to both Hate and Fear), *Desire* (akin to Lust), *Joy* (the Joyful Play of the new schema), and *Sorrow* (the equivalent of Panic/Grief and sorrow).

These primary emotions are evoked in many vertebrate species, our own species as well, by stimuli that impinge first upon a brain region

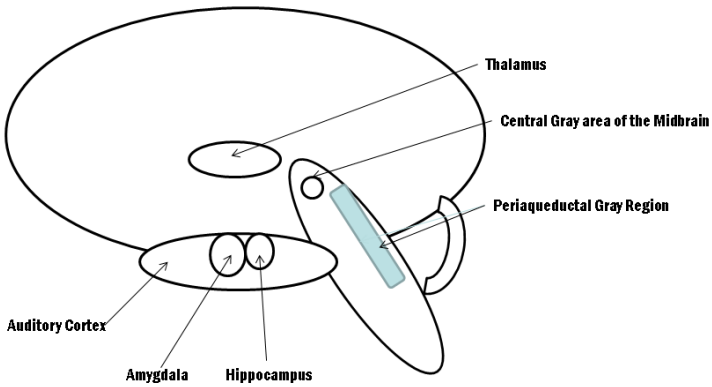
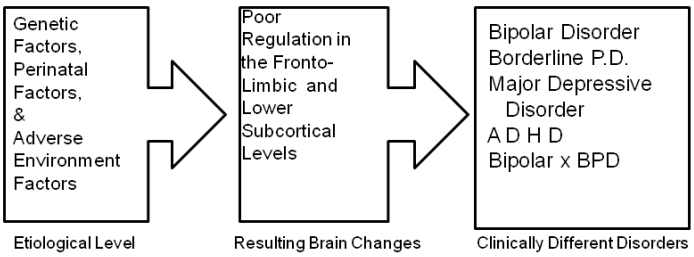


FIGURE 6.

in a subcortical layer deeper (and presumably older in evolutionary development) than the amygdala or other limbic centers; namely the *periaqueductal gray* (PAG), located in the dorsal aspect of the pons, near the inferior and superior colliculi, as depicted in Figure 6. Direct stimulation of various portions of the PAG in mammals can elicit any of the seven primary emotions, though the negative triad, fear, rage, and grief, register more strongly—from their sites in the dorsal portion of the PAG (Panksepp & Biven, 2012, p. 323).

The affective intensity of physical pain is also generated by those dorsal PAG sites, suggesting an evolutionary link, as to the organization of the brain, between raw *physical* pain and the *psychic* pain associated with fear and the other negative affects. The amygdala and the neocortical centers, in contrast, mediate the cognitive aspects of emotion—which involve (in us) the recognition in language of what affect we are experiencing. This recognition may come only moments after the raw affect is first registered in the PAG. From there the affect is communicated to the amygdala and on to the higher centers—allowing for verbal recognition and response. There is a connection between the activities of the deeper centers and what we refer to under the heading of "instinct." Panksepp and Biven offer the example of rats raised in a laboratory, never having been exposed to predators. If a piece of cat fur is introduced into their cage, they will react with fear: fearfulness being the unconditioned reaction to the unconditioned stimulus of the predator's smell (2012, p. 21). This can occur even in animals whose amygdalas have been ablated; a further indication of the primacy of the PAG, and of how certain reactions are built into the genome through evolu-



Key: At the "etiological" level there may be risk genes of bipolar disorder or ADHD, perinatal factors such as hypoxia at birth, or environment factors such as parental abuse or neglect. At the brain-change level there may be amygdala hyperactivity, prefrontal cortex changes, or hyperactivity at lower centers. The resulting disorders, seen as "different" clinically can include Bipolar Disorder, BPD, ADHD – singly or in different combinations.

FIGURE 7.

tion (p. 196). Perhaps the fear of snakes that most people experience also was "built in" to our genome, stemming from ancestral origins. We must often rely on animal research for analogies to human behavior; for obvious ethical reasons we cannot remove an infant's amygdala and test whether it still would recoil (because of a deeper center being stimulated) upon seeing a snake.

With these remarks as preparation, we can return to the matter at hand: BPD and other disorders as possible manifestations of hyperreactivity in brain regions subserving emotion. It will be useful in this regard to adopt a systems approach, in which the problem is analyzed into successive layers, each layer representing a different level of discourse, from the furthest-back etiological layer, upwards to the topmost layer of everyday clinical discourse. Viewed in this fashion, BPD and related conditions can be understood as the outward manifestations and phenomenological endpoints (endophenotypes, if you will) of processes set in motion by distal, and then by more proximate etiological factors. Such a schema is depicted in Figure 7.

At the *Distal Etiological Level* in the figure the panel is divided by a diagonal line: genetic factors in one section, adverse in fetal and environmental life in the other. The split via the diagonal line acknowledges that in some patients with an over-reactive disorder, risk genes play the larger role; in others, environmental factors and in still others, a combination of these influences.

At the *Proximal Etiological Level* dysregulation is an important factor—one that contemporary research has already shown to involve

changes in the ("bottom-up") limbic system and in key ("top-down") neocortical regions. Alterations in various neurotransmitter and neuropeptide levels play a role as well. Though less is known in humans, compared with information derived from animal studies, about deeper centers—especially the PAG—there is good reason to speculate that over-reactivity to certain stimuli may occur also in these deeper structures. In animal studies it is possible to insert probes into different subsections of the PAG, for example, and elicit one or another of the seven primary affective states—in the absence, that is, of any external stimulus (pleasant food, a predator threat, a sexual opportunity, etc.). Studying psychiatric disorders in the clinical situation we must rely (in trying to assess the weight of genetic factors, for example) on individuals free of adverse fetal-life and perinatal influences and free later on of disadvantageous family and other environmental (including head injury and brain disease) factors. Better still if such persons come from families where several close relatives suffered from a severe psychiatric disorder. Then, if a patient meeting these criteria developed BPD or a bipolar disorder (with or without BPD "comorbidity"), we would be on firmer ground to suspect that we were dealing with a condition brought about largely via genetic risk for the condition in question. From work with other mammals we have learned that the deeper centers, such as the PAG, may be the first line of defense, especially in relation to the negative affects, alerting the individual to external threat—before even the limbic and higher "thinking" parts of the brain join in the process.

At the clinical/descriptive level clinicians describe a number of psychiatric disorders that, although distinguishable in their various signs and symptoms, share a common feature: of brisk over-reactions to many stimuli, especially those pertinent to the interpersonal realm. Shown in Figure 7 as "balloons" overlying the panels for proximal and distal underlying factors, each appears as a descriptively separate entity, yet held together, as it were, by a collection of quite similar abnormalities in neurophysiology, neurotransmitters, and neuropeptides. It may be helpful to envision a picture of a child holding five balloons. If a photographer focused his lens only on the upper portion of the scene, we would see five different balloons—perhaps different in color also, but separate entities all the same. If the snapshot focused only on the lower half of the scene, we would see five strings all converging into the child's hand—emphasizing the "sameness" of whatever lay above.

The manner in which strikingly similar clinical pictures can stem from radically different antecedents can be demonstrated via the following two vignettes.

Vignette 1: A young woman was the only child of an affluent and highly educated couple. The mother's pregnancy had gone smoothly; she had abstained from alcohol throughout and took no drugs of any kind. There had been no birth complications; her Apgar after delivery was 10. The patient was sociable during her childhood and was academically gifted. Already at age 11 her skills in swimming earned her a spot in her school's junior swimming team. Her menarche, which came during the next year, ushered in abrupt changes: she became moody and unselfconfident, and was given to episodes of self-mutilation that on occasion necessitated brief hospitalizations. A few of these episodes in her later teens amounted to suicide gestures in severity, though she never took an overdose of prescribed or other pills, nor did she dabble in illicit drugs. Several psychiatrists diagnosed her as "borderline," mostly on the strength of the severity of the mutilative episodes, most of which occurred around the time of her menses. Because she often experienced severe pelvic pains at that time, endometriosis was suspected, though gynecological workup did not substantiate this. Eventually, her regimen was changed from antidepressants to a mood stabilizer, which proved effective in curbing the mutilative episodes. Several close relatives on both sides suffered from affective disorders, some characterized as "major depression"; others, as "bipolar disorder." The woman's general mood had shifted from "mainly depressed" to cheerful and exuberant, with only brief spells of gloominess, occurring, as before, around the time of her menses. A diagnosis of "bipolar II" now seemed more appropriate, now that the "borderline" elements were in abeyance.

Vignette 2: A woman in her early 30s sought help in a clinic because of her addiction to cocaine and marijuana. Little is known about the circumstances of her mother's pregnancy and delivery. Her parents came from a lower middle-class background. They divorced when the patient was two, following which she was in foster care until age four. She also was an only child. When returned to her father (her mother having disappeared in the meantime), he began molesting her sexually from when she was six until about ten. He raped her at gunpoint after immobilizing her with handcuffs. He would beat her repeatedly with either a belt or a wooden spoon, and would call her all manner of depreciatory names, cursing her with four-letter words. A schoolteacher, having finally noticed her bruises, reported the father to Child Protective Services. Investigation led to his being incarcerated—but only for a week, when his own mother bailed him out, the charges against him then being called "unfounded." During her adolescence, the patient took to cutting herself severely for which she was hospitalized on a number of occasions. She experienced nightmares and flashbacks, which prompted a diagnosis of posttraumatic stress disorder, besides BPD. Bereft of any family support, she turned to prostitution in her late teens, but later found a job as a receptionist in a restaurant. Her mood was one of moderate to severe depression, relieved partly by a regimen of antidepressants and a mood stabilizer (lamotrigine).

Both of the women in these vignettes were given, not without justification by current standards, the diagnosis of BPD. But in the woman of the first example, no postnatal, nor even "constitutional" (meaning: related to events of fetal life and delivery) factors could be detected which could be construed as having any etiological significance. There would appear to be no influences to which we could assign her development of "borderline" personality—apart from risk genes for some mental condition. Given her family history and her symptom display, the risk genes appear to have been those predisposing to bipolar disorder.

In the light of very recent developments on the psychogenetic side, however, we must be cautious even about that assessment, since the epochal study by the National Human Genome Research Institute, specifically, of its Psychiatric Genomics Consortium, gave evidence that actually five clinically different conditions are genetically linked (Serretti & Fabbri, 2013). The conditions in question include autism, attention-deficit hyperactivity disorder, clinical depression, bipolar disorder, and schizophrenia. Here again, we have five clinical "balloons" whose strings are held by one hand: the array of commonly shared genes, namely, the four single-nucleotide polymorphisms (SNPs) identified by the research group. The authors emphasized how key mental illness–related genes can predispose to any of the five clinical conditions, and that a particular patient may appear "bipolar" at one point in life and "schizophrenic" in another, depending on intervening life circumstances that nudge the outward clinical appearance now in this direction, now in that, during the life-course.

As for the patients in the last two vignettes: the borderline picture in the first woman appears to have derived from a particularly intense expression of genic vulnerability to mental illness (manifesting as bipolar disorder with accompanying BPD—until treatment ameliorated the BPD component and softened the bipolar aspects). In the second woman, it appears that we need look no further, as to causation, than to the appalling circumstances of her early years, granted that we do not know whether there had been mentally ill persons among her close relatives. The fact that she has not thus far appeared to suffer from any of the five disorders outlined by the genomic study suggests (but does no more than suggest) that genic vulnerability may not have played a large role in her evolution as a borderline patient.

The thrust of this article is on the *similarity* (not at the genetic level, but rather on the cerebral level) of peculiarities in the prefrontal and subcortical regions (both limbic and deeper) of the brain that conspire to promote the development of hyper-reactive mental disorders. Depending on various genetic and environmental factors, these disorders

may appear clinically different; namely, Borderline Personality Disorder, Bipolar Disorder, ttention-eficit disorder with hyperactivity, and perhaps intermittent explosive disorder, and also major expressive disorder (the first four having the clinical characteristic of *over-reactivity* to various significant stimuli).

A HISTORICAL NOTE

The idea that several, or even most, of the major mental illnesses may have much in common, as opposed to being distinctly different, has a long history. The Belgian psychiatrist, Joseph Guislain (1833), saw the erstwhile "different" conditions as better conceptualized as consecutive stages in the unfolding of what we would now call a psychosis. He felt the progression went from exaltation, on to aberration, then to oppression, and finally to exhaustion. These are akin to our mania, schizophrenia, depression, and dementia. He used the terms *hyperphrénie* and *paraphrénie* for the first two stages (our mania and schizophrenia). Hyperphrenia captures the notion of over-reactivity or hyperactivity that we associate with manic states within the bipolar disorders. Guislain's work was translated into German by the Württemburg psychiatrist, Ernst Albrecht Zeller, in a work he called the *Einheitspsychose* of "unitary psychosis."

He accepted the notion of different "stages," mentioning that in one case, all the different forms may occur. His theory was predicated on the belief in the unity of the soul, rather than on a more objectifiable study of the family histories of illness among various patients with a psychosis. Zeller's pupil, Wilhelm Griesinger (1871), though accepting the concept of a unitary psychosis, saw the underlying cause as a kind of reflex action of the nervous system: the brain was the primary site of mental illness, which appeared to progress (as Guislain, 1833, had proposed) from melancholia to mania and finally, dementia. In the latter part of the 19th century the concept of a unitary psychosis fell out of favor. Kahlbaum (1863), for example, asserted that mental disease could indeed be categorized into at least four varieties (acute, typical, progressive, and catatonic *vesania*) based on clinical descriptions. When studies of the mentally ill and their close relatives came into vogue in the 20th century, the clinically distinct psychoses were seen by some as related not by stages in the life-course, but by degree of *severity*. Maier (1992), for example, advocated a multifactorial model in which unipolar depression was seen as the least severe psychosis, mania next, then schizoaffective, and then as the most extreme, schizophrenia. Close relatives of each type had relatives *mostly* of the same type—but could

also have some relatives of the other three. But unipolar probands had the fewest relatives with schizophrenia; schizophrenic probands had the most. Vogel (1992) also noted how family studies suggested that relatives of persons with any of the four major types of psychosis might show any of the four types, but tended to "breed true," in the sense that bipolar probands had significantly more bipolar relatives than did probands with the other types; schizophrenic probands, more schizophrenic relatives, and so on (usually in the range of 5% to 8%, as against 1% to 2% of different-type relatives). But probands of *any of the four types* had a considerable excess of relatives with major depression (in the range of 20%). This led Vogel to conclude that there were most likely both certain genes in common to all four types, but also certain other genes that were more specific to just one of the four types. To that extent, there remained some utility in preserving the four categories, even though there appeared to be more in common from a genetic standpoint than was hitherto supposed within the psychiatric community. Vogel's paper of course antedated the report of Serretti and Fabbri by some 20 years.

SOME RECENT FAMILY AND GENETIC STUDIES

As for borderline personality disorder, the possibility of a genetic tendency to the condition has been studied by a number of investigators. Their work has been summarized by one of the more prominent researchers in this area: Sven Torgersen (2000) found, for example, that in his first (and small scale) twin study of 7 MZ and 18 DZ pairs, concordance was zero among the monozygotic pairs. But in his later and much larger twin study, concordance for BPD was considerable. Family (as opposed to twin) studies showed an apparent increase of BPD relatives among the families of BPD probands, though the figures tended to be inflated if one relied on reports by the patients themselves about their relatives, as opposed to data emerging from direct interviews with the relatives. Links, Steiner, and Huxley (1988) suspected that their BPD patients exaggerated the BPD features of their relatives, leading to an apparent 15% frequency—more than four times the 3.4% frequency when the relatives were interviewed by the research team. The frequency of bipolar persons in these studies was not mentioned. When the spotlight is on bipolar or cyclothymic disorders, in contrast, a different picture emerges. Those Bipolar II patients (i.e., with brief periods of manic excitement that are followed by longer periods of severe depression) tend to get labeled "borderline" rather than affectively ill (Akiskal & Pinto, 1999). Such a tendency would make the overlap re-

gion of BPD × Bipolar much smaller than it might be if clinicians were better attuned to the subtleties of bipolar and cyclothymic disorders.

ADD/H (or in some reports, ADHD) is also characterized by brain overactivity and impulsivity. In a recent meta-analysis of family genetic studies relative to ADHD and Bipolar type I disorder, a higher prevalence of ADHD was noted among relatives of bipolar probands; likewise, a higher prevalence of Bipolar Disorder was found among the relatives of ADHD probands. Relatives of bipolar I patients had a substantially greater risk for ADHD (nearly 30%) compared with the risk of bipolar I disorder among relatives of ADHD probands (approximately 5.5%; Faraone, Biederman, & Wozniak, 2012). In clinical samples ADHD has been present in the histories of many, especially male, patients with BPD. Several recent fMRI studies with ADHD patients have shown amygdala hyperactivity (Brotman et al., 2010) while rating subjective fear of neutral faces. Prefrontal dysfunction, manifested as decreased activation in the ventrolateral prefrontal cortex and in the right anterior cingulate, was found in the fMRI study of both ADHD and pediatric bipolar-disorder patients (Passarotti, Sweeney, & Pavuluri, 2010). These studies also point to similarities between bipolar, borderline, and ADHD patients in areas of brain reacting abnormally—both in the neocortex and in the limbic system, manifest in the latter as hyperarousal. Such findings bolster the hypothesis proposed here of similarities in brain function in otherwise (clinically) different psychiatric disorders.

While the impressions of Guislain and Zeller about a "unitary psychosis," harkening back to the early 19th century, were only hunches, or perhaps prejudices, not based on scientific evidence, as refinements in studying mental disorders have been made in the intervening years, strong similarities have been found linking several of the more important disorders—such as bipolar disorder, schizophrenia, ADHD, and BPD. These refinements began with family genetic studies, more recently with neuroimaging studies, and now even with molecular-genetic studies by the Genomic Consortium group. These studies have helped move us beyond the clinical-descriptive level—ever closer to an understanding at the level of underlying etiology of the severe mental disorders.

In relation to BPD, we can now begin to see that within the broad heterogeneous domain of clinical BPD, there exists a subset that is closely linked to bipolar disorder, and this in two main ways: first, certain patients with strong genetic vulnerability to bipolar disorder go on to develop concomitant BPD, even in the absence of early abuse and other adverse environmental experiences. Sometimes the BPD is clinically apparent before the bipolar symptoms; sometimes, the bipolar disorder is noted earlier. Second, severe abuse can by itself, via epigenetic influ-

ences, lead to BPD. And this can happen (as portrayed in Figure 2) in the absence of an underlying bipolar condition (the more common situation), or the abuse can exaggerate the impact of a pre-existing bipolar vulnerability.

In general among the *overactive* psychiatric disorders, comorbidities are common. Post and Kalivas (2013) underline this in relation to bipolar disorder—where substance abuse is a common accompaniment. Not only that, but abuse, particularly of the stimulant drugs (cocaine, amphetamine, methamphetamine, phencyclidine), "increases motor hyperactivity and stereotypy rather than a tolerance pattern of adaptation and decreased behavioral response" (p. 173), each condition intensifying the impact of the other. They refer to this phenomenon as cross-sensitization. One could add *BPD* as another consequence, potentially, of substance abuse when the latter occurs in persons predisposed by virtue of childhood *conduct disorder* (cf. Freestone et al., 2013), the latter often evolving into antisocial personality. Conduct disorder, meanwhile, is itself a common clinical accompaniment of an underlying *ADHD*—the heritability of which appears to be greater than was formerly thought (Chang, Lichtenstein, Asherson, & Larsson, 2013). But risk genes for ADHD not only predispose to conduct disorder, but also, if the two are present together, to future BPD and Antisocial Personality (ASPD). The BPD × ASPD combination is particularly frequent in male patients who show antisocial features with violent tendencies, and also in female patients who get remanded to forensic hospitals for violent behavior (Freestone, Howard, Coid, & Ullrich, 2013).

These remarks point to interactions among the conditions under discussion here: BPD, bipolar disorder, and ADHD, whose intensity at the clinical level (whether seen as separate entities or as comorbid agglomerations) can be magnified or aggravated by child abuse, childhood conduct disorder, and adolescent substance abuse. All the resulting psychiatric disorders can be subsumed under the rubric of overactive/hyperactive conditions. They are characterized by poor inhibitory control from the neocortex, and by rapid, impulsive, maladaptive, and at times violent responses to external stimuli of a sort that elicit strong emotion. And, as we have proposed here, to someone peering only into the frontal lobes, the limbic system, and deeper subcortical regions like the periaqueductal gray (and not paying much attention to external clinical behaviors), the conditions seem eerily similar, akin to the common-gene hypothesis being elaborated for the major psychoses. The situation with the disorders highlighted here is mirrored in the recent remark by Dr. Henry Nasrallah, editor of *Current Psychiatry*, who spoke, under the heading of *pleiotropy*, about the way in which one gene can influence multiple clinical phenotypic traits (Nasrallah,

2013). He predicted that many psychiatric conditions currently seen as separate in *DSM* will soon be recognized as "interrelated components of a syndrome" (p. 6). In particular he singled out the five conditions mentioned above, from the work of Serretti and Fabbri—two of which (ADHD and bipolar disorder) have been addressed in this article.

The various interactions of the *over-reactive* disorders, which also include BPD and certain cases of antisocial personality, can be understood also from a developmental perspective. Risk genes promoting the development of bipolar disorder or ADHD may include some common to both, and probably others that conduce to rendering the clinical conditions more distinguishable. In early life one may see (clinical) ADHD or conduct disorder—either of which can be aggravated by child abuse or illicit drugs. Finally, in the late teens or early 20s, we may see a variety of conditions, singly or in combination, such as (continuing) ADHS, BPD, bipolar disorder (whether type I or II), and Antisocial Personality.

Clinically, one may encounter patients in whom *all* the over-active conditions coexist: some emerging in childhood and adolescence; others become recognizable a few years later in early adult life. The following vignette is an example.

> A man of 50 was hospitalized at a forensic center following an arrest for reckless endangerment and attempted murder. He had fired a shotgun in a crowded nightclub, injuring no one but damaging the bar. He claimed he was trying to close a place down that trafficked in drugs and prostitution. Recently he had been discharged from a conventional psychiatric hospital, where he had been treated for bipolar disorder. He stopped taking his mood-stabilizing medications once he left the hospital.
>
> Notably hyperactive as a child, and unmanageable at home because of his disruptive and disobedient behavior, he was diagnosed with ADHD and conduct disorder at age seven. He set fires, tortured animals, besides destroying property at home. In adolescence he raped his younger sister and attempted to murder his father with a knife. From early childhood, his mother—a violent and abusive woman hospitalized on several occasions for bipolar disorder—beat the patient severely, burned his hands on the stove as punishment and cut him with a meat cleaver. Thrown out of the home at 14, he lived by his wits, via theft and selling drugs. He began abusing a variety of drugs, including alcohol, marijuana, cocaine, LSD, phencyclidine ("angel dust"), amphetamines, and mescaline. These made him paranoid and more aggressive, but there were also periods of depression in which he made suicide attempts and gestures: hanging, wrist-cutting, and overdoses. Hospitalized at 19, he was diagnosed with bipolar disorder, borderline personality disorder, and antisocial personality. Many psychiatric hospitalizations and incarcerations in prison followed. He was often belligerent and combative at these institutions, assaulting staff members and other inmates.

Assessment of brain structures (via, for example, single photon emission computed tomography [SPECT] or fMRI) were not performed on this patient, so information is lacking in regard to any abnormalities in neocortical and limbic structures. What is of interest nonetheless is the confluence in one person of all the common psychiatric conditions associated with hyperactivity and over-reactive brain responsivity. Given that the mother was bipolar, it is likely that the patient similarly carried risk-genes for that condition. Whether his was a case of bipolar disorder predisposing to childhood ADHD, or whether his ADHD stemmed from a separate set of risk-genes for that condition is unclear. But the bipolar disorder appears as the primary condition, giving rise to other overactive forms of emotional dysregulation: conduct disorder in childhood; BPD and an aggressive form of antisocial personality disorder later on, all aggravated since adolescence by chronic abuse of stimulating and "mind-altering" drugs.

COMMENTS

With respect to the two major overactive conditions, bipolar disorder and borderline personality disorder, we are now in a better position to resolve the controversy about their relationship. While it is incorrect to claim, taking the "lumper" position, that BPD is a subtype of bipolar disorder, it is also incorrect to take the "splitter" position, asserting that they are unrelated. Data from brain-imaging research makes it more reasonable to state that within the domain of bipolar disorder there is an important *subset* of patients with concomitant BPD existing as two sides of the same coin, united by strong similarities in abnormalities or peculiarities in the neocortex and the limbic system. The BPD component, when present, can arise either as an endophenotype reflecting either unusually strong genetic vulnerability to bipolar disorder in the absence of early environment abuse (or other adverse life events), or, as a manifestation of markedly adverse life events in a patient with only modest bipolar predisposition. The overlap region for the two conditions, given the presence of BPD (i.e., the subset: *Bipolar* × *BPD*), will vary in size from one patient sample to another: rare in some samples (favoring the prejudices of the splitters); common in other samples (favoring the prejudices of the lumpers). In a similar way, imaging researchers studying bipolar patients may implicate certain prefrontal cortex areas as the most important (e.g., the inferior frontal gyrus and its role in emotional regulation and social-emotional learning; Hayek, 2012). Those working primarily with BPD patients may point to the same region (Domes, Schulze, & Herpertz, 2009). In a like

fashion, amygdala hyperactivity to fearful faces has been noted both in bipolar patients (Garrett et al., 2012; Kim et al., 2012) and in BPD (the reports of Ruocco et al. and of Weninger et al. cited above). The connection between ADHD and either bipolar disorder or BPD is perhaps less strong than that between bipolar disorder and BPD, though a history of ADHD is fairly common in either group of (adult) patients. Amygdala hyperactivity has also been noted in a recent study of ADHD adolescents, akin to that noted in bipolar disorder and BPD (Posner et al., 2011). Panksepp's data from the study of other mammals suggests, in any event, that the site more responsible than the amygdala for the generation of raw emotional feelings is the periaqueductal gray (PAG)—less accessible, however, for direct study in humans (Watt & Panksepp, 2009). Because the emotional system in mammals goes along the pathway PAG to Amygdala to Neocortical Centers, it will be an important topic for future research to evaluate the role of the PAG, particularly with a view to determining whether it is hyperactive in borderline and bipolar patients. This question looms all the more importantly in those patients in whom BPD can be understood as an epiphenomenon of strong genetic predisposition to bipolar disorder, especially where adverse environmental factors are not present.

TREATMENT IMPLICATIONS

The diversity of clinical pictures subsumed under the rubric of BPD argues against the advocacy of any particular treatment program as being universally applicable. Clinicians are often alerted to the diagnosis via the impulsive and self-destructive behaviors of a patient they are evaluating initially. Limit-setting interventions will usually be necessary in the beginning, including those directed against suicidal tendencies. The latter are accompanied by significant levels of depression and anxiety in most instances. Hospitalization may be indicated at times, but symptom relief via medication will be necessary at the outset in the majority of cases. The tempestuous emotionality, typically in the form of rage outbursts or else self-directed rage leading to suicidal or self-mutilative acts, is often better relieved by mood-stabilizing medications than by antidepressants. This is especially true in the subset within the borderline domain—where an underlying bipolar disorder is the major causative factor: namely, in the *Bipolar* × *BPD* realm. The more common picture clinically will be one of *Bipolar II* × *BPD*; that is, hypomanic episodes with deeper depressive episodes, alongside the "borderline" attributes. In the more severe cases, however, where suicidality and self-mutilation dominate the clinical picture, mood stabilizers may have to

be buttressed by a neuroleptic medication. The newer generation of conventional compounds, such as olanzapine and risperidone, may not always suffice. When that is so, reliance on clozapine may prove invaluable. Clozapine, which was recommended originally only for schizophrenia, has shown effectiveness in bipolar disorder as well. This may relate to its dual action—on both dopamine and also serotonin receptors, with greater activity in the limbic than on striatal receptors. These attributes of clozapine may in turn contribute to its known effectiveness in reducing the tendency to suicidal and other self-destructive behaviors (Nielsen, Kane, & Correll, 2012), though there is a need now for randomized-controlled studies to test further clozpapine's efficacy (Poon, Sim, Sum, Kuswanto, & Baldessarini, 2012). Meanwhile, some have stated that clozapine appears to be more appropriate for bipolar and schizoaffective patients than for schizophrenic patients (Vacheron-Trystam, Braitman, Cheref, & Auffray, 2004).

In the overall treatment of patients showing the bipolar-BPD picture, it is generally accepted that a combined pharmacological and psychotherapeutic approach is optimal. The point here is that in the most severe, and life-threatening cases, the less well-recognized and less often utilized pharmacological agents, clozapine, in particular, may prove effective—and life-saving—where other medications have failed. It remains to be seen whether the genes now believed to link several of the "overactive" conditions mentioned above (Serretti & Fabbri, 2013) also predispose to the formation of the similar brain changes that appear to underlie these conditions: bipolar disorder, BPD when linked to bipolar disorder, and ADHD. If this proved true, it may point the way to the development of more specific and effective pharmacological remedies for those aspects of the disorders that cannot be controlled adequately by psychotherapy alone.

REFERENCES

Akiskal, H. S. (1981). Subaffective disorders: Dysthymic, cyclothymic and bipolar-II disorders in the "borderline" realm. *Psychiatric Clinics of North America, 4*, 25-46.

Akiskal, H. S., & Pinto, O. (1999). The evolving bipolar spectrum. Prototypes I, II, III, and IV. *Psychiatric Clinics of North America, 22*(3), 517-534.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Benazzi, F. (2006). Borderline personality-bipolar spectrum relationship. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 30*, 68-74.

Benazzi, F. (2008). A relationship between bipolar-II disorder and borderline personality disorder? *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 32*, 1022-1029.

Bouchard, S., Lemelin, S., Dubé, C., & Giguère, J. F. (2010). Dysregulation of the executive system and theory of mind: Clinical interest of a neuroscientific conception of BPD. *Santé Mentale Québec, 35*, 227-251.

Brendel, G. R., Dtern, E., & Silbersweig, D. A. (2005). Defining the neurocircuitry of borderline personality disorder: Functional neuroimaging approaches. *Development and Psychopathology, 17*, 1191-1206.

Brotman, M. A., Rich, B. A., Guyer, A. E., Lunsford, J. R., Horsey, S. E., Reising, M. M., et al. (2010). Amygdala activation during emotion processing of neutral faces in children with severe mood dysregulation versus ADHD or bipolar disorder. *American Journal of Psychiatry, 167*, 61-69.

Chang, Z., Lichtenstein, P., Asherson, P. J., & Larsson, H. (2013). Developmental twin study of attention problems. *JAMA Psychiatry* [formerly *Archives of Psychiatry*], *70*, 311-318.

Coccaro, E. F., McCloskey, M. S., Fitzgerald, D. A., & Phan, K. L. (2007). Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. *Biological Psychiatry, 62*, 168-178.

Coccaro, E. F., Sripada, C. S., Yanowitch, R. N., & Phan, K. L. (2011). Corticolimbic function in impulsive aggressive behavior. *Biological Psychiatry, 69*, 1153-1159.

Depue, R. A., & Fu, Y. (2012). Modeling borderline personality disorder based on the neurobehavioral foundation of major personality traits. *Psychodynamic Psychiatry, 40*, 131-180.

Descartes, R. (1650). *Passiones animae*. Amsterdam: Ludwig Elzevir.

Domes, G., Schulze, L., & Herpertz, S. C. (2009). Emotion recognition in borderline personality disorder: A review of the literature. *Journal of Personality Disorders, 23L*, 6-19.

Faraone, S. V., Biederman, J., & Wozniak, J. (2012). Examining the comorbidity between attention deficit hyperactivity disorder and bipolar I disorder: A meta-analysis of family genetic studies. *American Journal of Psychiatry, 169*, 1256-1266.

Freestone, M., Howard, R., Coid, J. W., & Ullrich, S. (2013). Adult antisocial syndrome co-morbid with borderline personality disorder, substance dependence and violent antisociality. *Personality and Mental Health, 7*, 11-21.

Garrett, A. S., Reiss, A. L., Howe, M. E., Kelley, R. G., Singh, M. K., Adelamn, N. E., Karchemskiy, A., & Chang, K. D. (2012). Abnormal amygdala and prefrontal cortex activation to facial expressions in pediatric bipolar disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*, 821-831.

Griesinger, W. (1871). *Die pathologie und therapie psychischen krankheiten fuer AErzte und studirende* (3rd ed.). Braunschweig: F. Wreden.

Guislain, J. (1833). *Traité des phrénopathies ou doctrine nouvelle des maladies mentales*. Brussels.

Gunderson, J. G. (2001). *Borderline personality disorder: A clinical guide*. Washington, DC: American Psychiatric Publishing.

Hayek, T. (2012). Brain-region size may be long-sought biomarker. *Psychiatric News*, Sept. 21.

Hughes, A. E., Crowell, S. E., Uyeiji, L., & Coan, J. A. (2012). A developmental neuroscience of borderline pathology: Emotion dysregulation and social baseline theory. *Journal of Abnormal Child Psychology, 40*, 21-33.

Irle, E., Lange, C., Weninger, G., & Sachsse, U. (2007). Size abnormalities of the superior parietal cortices are related to dissociation in borderline personality disorder. *Psychiatry Research, 156*, 139-149.

Kahlbaum, K. L. (1863). *Die gruppierung der psychischen krankheiten und die einheilung der seelenstörungen.* Danzig: Kafemann.

Kim, P., Thomas, L. A., Rosen, B. H., Moscicki, A. M., Brotman, M. A., Zarate, C. A. Jr., Blair, R. J., Pine, D. S., & Leibenluft, E. (2012). Differing amygdala responses to facial expressions in children and adults with bipolar disorder. *American Journal of Psychiatry, 169*, 642-649.

Links, P. S., Steiner, M., & Huxley, G. (1988). The occurrence of borderline personality disorder in the families of borderline patients. *Journal of Personality Disorders, 2*, 14-20.

Mackinnon, D. F., & Pies, R. (2006). Affective instability as rapid cycling: Theoretical and clinical implications for borderline personality and bipolar spectrum disorders. *Bipolar Disorder, 8*, 1-14.

Magill, C. A. (2004). The boundary between borderline personality disorder and bipolar disorder: Current concepts and challenges. *Canadian Journal of Psychiatry, 49*, 551-556.

Maier, W. (1992). Kontinuität und diskontinuität funktioneller psychosyndrome im lichte von familienstudien. In C. Mundt & H. Sass (Eds.), *Für und wider die einheitspsychose* (pp. 99-109). Stuttgart: G. Thieme.

Minzenberg, M. J., Fan, J., New, A. S., Tang, C. Y., & Siever, L. J. (2007). Fronto-limbic dysfunction in response to facial emotions in borderline personality disorder: An event-related fMRI study. *Psychiatry Research, 155*, 231-243.

Nasrallah, H. (2013). Pleiotropy of psychiatric disorders will reinvent *DSM*. *Current Psychiatry, April*, 6-7.

New, A. S., Goodman, M., Triebwasser, J., & Siever, L. J. (2008). Recent advances in the biological study of personality disorders. *Psychiatric Clinics of North America, 31*, 441-461.

Nielsen, J., Kane, J. M., & Correll, C. U. (2012). Real-world effectiveness of clozapine in patients with bipolar disorder: Results from a 2-year mirror-image study. *Bipolar Disorder, 14*, 863-869.

O'Neill, A., & Frodi, T. (2012). Brain structure and function in borderline personality disorder. *Brain Structure and Function, 217*, 767-782.

Pally, R. (2002). The neurobiology of borderline personality disorder: The synergy of "nature and nurture." *Journal of Psychiatric Practice, 8*, 133-142.

Panksepp, J., & Biven, L. (2012). *The archaeology of mind: Neuroevolutionary origins of human emotions*. New York: Norton.

Passarotti, A. M., Sweeney, J. A., & Pavuluri, M. N. (2010). Neural correlates of response inhibition in pediatric bipolar disorder and attention deficit hyperactivity disorder. *Psychiatry Research, 181*, 36-43.

Perugi, G., Angst, J., Azorin, J. M., Bowden, C., Vieta, E., Young, A. H., & the BRIDGE Study Group. (2013). The bipolar-borderline personality connection in major depressive patients. *Acta Psychiatrica Scandinavica, 124*, 1-8.

Poon, S. H., Sim, K., Sum, K. Y., Kuswanto, C. N., & Baldessarini, R. J. (2012). Evidence-based options for treatment-resistant adult bipolar patients. *Bipolar Disorder, 14*, 573-584.

Posner, J., Nagel, B. J., Maia, T. V., Mechling, A., Oh, M., Wang, Z., & Peterson, B. S. (2011). Abnormal amygdalar activation and connectivity in adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 50*, 828-837.

Post, R. M., & Kalivas, P. (2013). Bipolar disorder and substance misuse: Pathological and therapeutic implications of their comorbidity and cross-sensitization. *British Journal of Psychiatry, 202*, 172-176.

Prossin, A. R., Love, T. M., Koeppe, R. A., Zubieta, J. K., & Silk, K. R. (2010). Dysregulation of regional endogenous opioid function in borderline personality disorder. *American Journal of Psychiatry, 167*, 925-933.

Radaelli, D., Poletti, S., Dallspezia, S., Colombi, C., Smeraldi, E., & Benedetti, F. (2012). Neural responses to emotional stimuli in comorbid borderline personality disorder and bipolar depression. *Psychiatry Research, 203*, 61-66.

Riggs, A. D., Russo, V. E. A., & Martienssen, R. A. (1996). *Epigenetic mechanisms of gene regulation*. Plainview, NY: Cold Spring Harbor Laboratory Press.

Rihmer, Z., & Benazzi, F. (2010). Impact of suicidality of the borderline personality traits: Impulsivity and affective instability. *Annals of Clinical Psychiatry, 22*, 121-128.

Rodriques, E., Wenzel, A., Ribeiro, M. P., Quanrantini, L. C., Miranda-Scrippa, A., de Sena, E. P., & de Oliveira, I. R. (2011). Hippocampal volume in borderline personalty disorder, with and without comorbid post morbid. *European Psychiatry, 26,* 452-456.

Ruocco, A. C., Amirthavasagam, S., & Zakzanis, K. K. (2012). Amygdala and hippocampal volume reductions as candidate endophenotypes for borderline personality disorder: A meta-analysis of magnetic resonance imaging studies. *Psychiatry Research, 201*, 245-252.

Schmahl, C. G., McGlashan, T. H., & Bremmer, J. D. (2002). Neurobiological correlates of borderline personality disorder. *Psychopharmacology Bulletin, 36*, 69-87.

Serretti, A., & Fabbri, C. (2013). Shared genetics among major psychiatric disorders. *Lancet.* Early Online Publication, 28 Feb. 2013. doi: 10.1016/S0140-6736(13)60223-8

Siever, L. J. (2008). Neurobiology of aggression and violence. *American Journal of Psychiatry, 165*, 429-442.

Siever, L. J., & Weinstein, L. N. (2009). The neurobiology of personality disorders: Implications for psychoanalysis. *Journal of the American Psychoanalytic Association, 57*, 361-398.

Stanley, B., & Siever, L. J. (2010). The interpersonal dimension of borderline personality disorder: Toward a neuropeptide model. *American Journal of Psychiatry, 167*, 24-39.

Stone, M. H. (1979). Modern concepts of emotion as prefigured in Descartes "Passions of the Soul." *Journal of the American Academy of Psychoanalysis, 8*, 473-495.

Stone, M. H. (1980). *The borderline syndromes*. New York: McGraw Hill.

Stone, M. H. (1981). Borderline syndromes: A consideration of subtypes and an overview. *Psychiatric Clinics of North America, 4*, 3-24.

Stone, M. H. (1988). Toward a psychobiological theory of borderline conditions. *Dissociation, 1*, 1-15.

Stone, M. H. (1990). *The fate of borderlines*. New York: Guilford.
Stone, M. H. (2012). Disorder in the domain of the personality disorders. *Psychodynamic Psychiatry, 40*, 23-45.
Torgersen, S. (2000). Genetics of patients with borderline personality disorder. *Psychiatric Clinics of North America, 23*(1), 1-9.
Vacheron-Trystam, M. N., Braitman, A., Cheref, S., & Auffray, L. (2004). Antipsychotics in bipolar disorders. *Encephale, 30*, 417-424.
Vogel, F. (1992). Für und wider die einhetispsychose aus genetischer sicht. In C. Mundt & H. Sass (Eds.), *Für und wider die einheitspsychose* (pp. 110-119). Stuttgart: G. Thieme.
Watt, D. F., & Panksepp, J. (2009). Depression: An evolutionarily conserved mechanism to terminate separation-distress? A review of aminergic, peptidergic and neural network perspectives. *Neuropsychoanalysis, 11*, 5-104.
Weninger, G., Lange, C., Sachsse, U., & Irle, E. (2009). Reduced amygdala and hippocampus size in trauma-exposed women with borderline personality disorder and without post-traumatic stress disorder. *Journal of Psychiatry and Neuroscience, 34*, 383-388.
Widiger, T. A., & Costa, P. T. Jr. (2013). Personality disorders and the Five Factor Model of personality: Rationale for the 3rd edition. In T. A. Widiger & P. T. Costa, Jr. (Eds.), *Personality disorders and the Five Factor Model of personality* (3rd ed., pp. 3-11). Washington, DC: American Psychological Press.
Wingenfeld, K., Spitzer, C., Rullkötter, N., & Löwe, B. (2010). Borderline personality disorder: Hypothalamus pituitary adrenal axis and findings from neuroimaging studies. *Psychoneuroendocrinology, 35*, 154-170.
Zeller, A. E. (1840). Die einheitspsychose. *Medizinische Korrespondenzblätter der Württemburgischen Medizinvereins, 10*, 17.

225 Central Park West
New York, NY 10024
mhstonemd@yahoo.com