The prevailing view among many psychiatrists and mental health professionals is that borderline personality disorder (BPD) is a “psychological” condition. BPD often is conceptualized as a behavioral consequence of childhood trauma; treatment approaches have emphasized intensive psychotherapeutic modalities, less so biologic interventions. You might not be aware that a large body of research over the past decade provides strong evidence that BPD is a neurobiological illness—a finding that would drastically alter how the disorder should be conceptualized and managed.

Neuropathology underpins the personality disorder

Foremost, BPD must be regarded as a serious, disabling brain disorder, not simply an aberration of personality. In DSM-5, symptoms of BPD are listed as: feelings of abandonment; unstable and intense interpersonal relationships; unstable sense of self; impulsivity; suicidal or self-mutilating behavior; affective instability (dysphoria, irritability, anxiety); chronic feelings of emptiness; intense anger episodes; and transient paranoid or dissociative symptoms. Clearly, these clusters of psychopathological and behavioral symptoms reflect a pervasive brain disorder associated with abnormal neurobiology and neural circuitry that might, at times, stubbornly defy therapeutic intervention.

No wonder that 42 published studies report that, compared with healthy controls, people who have BPD display extensive cortical and subcortical abnormalities in brain structure and function. These anomalous patterns have been detected across all 4 available neuroimaging techniques.

Magnetic resonance imaging. MRI studies have revealed the following abnormalities in BPD:
- hypoplasia of the hippocampus, caudate, and dorsolateral prefrontal cortex
- variations in the CA1 region of the hippocampus and subiculum
- smaller-than-normal orbitofrontal cortex (by 24%, compared with healthy controls) and the mid-temporal and left cingulate gyri (by 26%)
- larger-than-normal volume of the right inferior parietal cortex and the right parahippocampal gyrus
- loss of gray matter in the frontal, temporal, and parietal cortices
- an enlarged third cerebral ventricle
- in women, reduced size of the medial temporal lobe and amygdala
- in men, a decreased concentration of gray matter in the anterior cingulate
- reversal of normal right-greater-than-left asymmetry of the orbitofrontal cortex gray matter, reflecting loss of gray matter on the right side
- a lower concentration of gray matter in the rostral/subgenual anterior cingulate cortex
- a smaller frontal lobe.

BPD must be regarded as a serious, disabling brain disorder, not simply an aberration of personality and behavior.
In an analysis of MRI studies, correlation was found between structural brain abnormalities and specific symptoms of BPD, such as impulsivity, suicidality, and aggression. These findings might someday guide personalized interventions—for example, using neuro-stimulation techniques such as repetitive transcranial magnetic stimulation and deep brain stimulation—to modulate the activity of a given region of the brain (depending on which symptom is most prominent or disabling).

**Magnetic resonance spectroscopy.** In BPD, MRS studies reveal:
- compared with controls, a higher glutamate level in the anterior cingulate cortex
- reduced levels of N-acetyl aspartate (NAA; found in neurons) and creatinine in the left amygdala
- a reduction (on average, 19%) in the NAA concentration in the dorsolateral prefrontal cortex.

**Functional magnetic resonance imaging.** From fMRI studies, there is evidence in BPD of:
- greater activation of the amygdala and prolonged return to baseline
- increased functional connectivity in the left frontopolar cortex and left insula
- decreased connectivity in the left cuneus and left inferior parietal and the right middle temporal lobes
- marked frontal hypometabolism
- hypermetabolism in the motor cortex, medial and anterior cingulate, and occipital and temporal poles
- lower connectivity between the amygdala during a neutral stimulus
- higher connectivity between the amygdala during fear stimulus
- deactivation of the opioid system in the left nucleus accumbens, hypothalamus, and hippocampus
- hyperactivation of the left medial prefrontal cortex during social exclusion
- more mistakes made in differentiating an emotional and a neutral facial expression.

**Diffusion tensor imaging.** DTI white-matter integrity studies of BPD show:
- a bilateral decrease in fractional anisotropy (FA) in frontal, uncinated, and occipitofrontal fasciculi
- a decrease in FA in the genu and rostrum of the corpus callosum
- a decrease in inter-hemispheric connectivity between right and left anterior cingulate cortices.

**Genetic studies**
There is substantial scientific evidence that BPD is highly heritable—a finding that suggests that brain abnormalities of this disorder are a consequence of genes involved in brain development (similar to what is known about schizophrenia, bipolar disorder, and autism).

A systematic review of the heritability of BPD examined 59 published studies that were categorized into 12 family studies, 18 twin studies, 24 association studies, and 5 gene-environment interaction studies. The authors concluded that BPD has a strong genetic component, although there also is evidence of gene-environment (G×E) interactions (ie, how nature and nurture influence each other).

The G×E interaction model appears to be consistent with the theory that expression of plasticity genes is modified by childhood experiences and environment, such as physical or sexual abuse. Some studies have found evidence of hypermethylation in BPD, which can exert epigenetic effects. Childhood abuse might, therefore, disrupt certain neuroplasticity genes, culminating in morphological, neurochemical, metabolic, and white-matter aberrations—leading to pathological behavioral patterns identified as BPD.
The neuropsychiatric basis of BPD must guide treatment

There is no such thing as a purely psychological disorder. Invariably, it is an abnormality of brain circuits that disrupts normal development of emotions, thought, behavior, and social cognition. BPD is an exemplar of such neuropsychiatric illness, and treatment should support psychotherapeutic approaches to mend the mind at the same time it moves aggressively to repair the brain.

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