Bipolar I Disorder (BP-1) and the Brain

Bipolar I disorder (BP-1) is a complex and heterogeneous illness characterized by shifts in mood episodes, including mania, depression, and mixed states, as well as cognitive and psychomotor disturbances. Advances in neuroimaging have helped characterize structural and functional changes in specific brain regions and neural networks thought to be involved in emotion regulation, cognitive control, and motor function.[1]

Regions of the Brain Implicated in BP

Specific regions of the brain are hypothesized to regulate processes that may lead to the presentation of symptoms associated with BP-1.[2]

Emotional Homeostasis

Dysfunctions of the **dorsal and ventral systems** are thought to lead to a disruption of homeostasis in emotional processing, potentially resulting in mood instability in BP-1.[2]

- The dorsal system comprises the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), and the hippocampus.
- The ventral system consists of the insula, the amygdala, and the ventral striatum.

Anterior Cingulate Cortex

The ACC is thought to integrate information processing at the intersection of dorsal (cognitive) and ventral (emotional) prefrontal functions. Some studies suggest that left-sided hyperactivity of the ACC may be associated with mania, while hypoactivity of the ACC may be observed during bipolar depression.[3,4]

Hippocampus

The hippocampus is thought to be involved in memory and mood regulation. Imaging studies have shown that gray matter volume in the hippocampus is commonly reduced in patients with BP.[2,5]

- Functional magnetic resonance imaging (fMRI) findings have shown that patients with mania had decreased activity in the right hippocampus and parahippocampal gyrus during cognitive- and emotion-associated tasks when compared to individuals without BP-1 and patients with BP-1 in euthymia.[4]

Prefrontal Cortex

The PFC is thought to be a key region in the regulation of emotion and cognitive function. Reduced activity and structural changes in the PFC have been associated with BP. These changes may contribute to impulse control issues, emotional dysregulation, and impaired executive function.[4]

- Mania has been associated with a reduction in gray matter in the PFC. Longitudinal studies have shown that cortical thinning, in terms of volume and thickness, occurs more rapidly in the PFC of patients who had experienced more manic episodes over time. Inter-episodic euthymia was associated with no structural change or even an increase in gray matter.[6]
- Neuroimaging studies show that the PFC exhibits reduced activity in patients experiencing mania, especially in the right hemisphere, under specific cognitive and decision-making circumstances.[4]

Amygdala

The amygdala, a structure thought to generate fight-or-flight responses to threats, is thought to be involved in emotional regulation. fMRI studies of patients with BP have shown dysfunction in the amygdala.[3]

- Left amygdala hyperactivity has been implicated in emotional hypersensitivity and heightened arousal associated with manic episodes of BP-1.[4,7,8]
- Research suggests that activity in the amygdala is dysregulated in mania, with most studies suggesting increased activity in the left hemisphere or decreased activity on the right.[4]
- Variations in the direction of abnormalities exist in the literature: independent of the direction, amygdala activation and function appear to be disturbed/abnormal in response to emotional stimuli.[3]

Basal Ganglia

The basal ganglia are believed to regulate motor functions and emotional behaviors. The dopamine-driven basal ganglia-thalamo-cortical motor circuit plays a key role in psychomotor functions.[2,4]

- Imaging studies in individuals with BP have shown reductions in white matter integrity in the connections linking the thalamus, basal ganglia, and PFC. These reductions in white matter integrity were shown to be correlated with psychomotor retardation during depressive episodes and increased motor activity during manic episodes.[1] Additionally, available evidence suggests increased activity in the left basal ganglia is implicated in mania.[4]

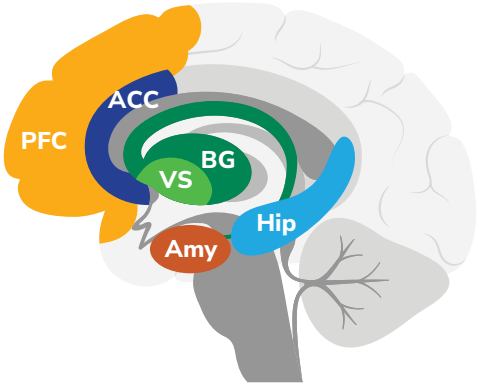
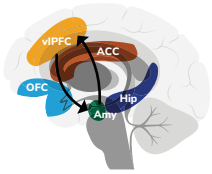


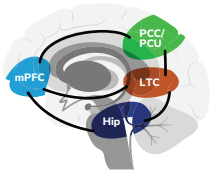
Figure 1. Regions of the brain implicated in BP-1.[9-12] Adapted from Su YA, et al. *Gen Psychiatr.* 2022;35:e100724. ACC = anterior cingulate cortex, Amy = amygdala, BG = basal ganglia, Hip = hippocampus, PFC = prefrontal cortex, VS = ventral striatum.

Key Neural Circuits Thought to Regulate BP-1 Symptoms

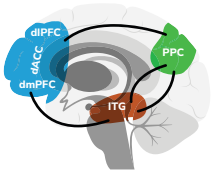
Disruptions in large-scale brain networks may be associated with various symptoms of BP-1, including mood instability, cognitive impairment, and psychomotor symptoms **(Figure 2)**.[2]



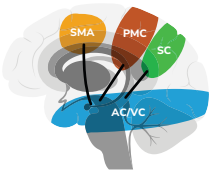
The **Fronto-limbic Neural Network** (FLN) consists of brain structures thought to be involved in regulating emotional responses. Disturbances in the fronto-limbic neural network may underlie the emotional instability in BP.[1]



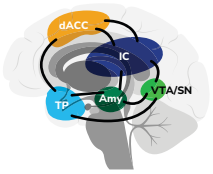
The **Default Mode Network** (DMN) is hypothesized to play a key role in self-referential thought and resting-state cognitive functions. It is thought to play a critical role in the emotional dysregulation characteristic of BP. Functional imaging studies have shown hyperactivation of the DMN in bipolar depression.[1]



The **Central Executive Network** (CEN) is thought to be critical to higher-order cognitive functions. Studies have shown underactivity of the CEN in patients with BP during cognitive tasks that require sustained attention and executive control.[1]



The **Sensorimotor Network** (SMN) is a primary integrator of sensory input and motor output. It is also associated with hyperactivity and psychomotor agitation in a manic phase and with hypoactivity and psychomotor retardation in a depressive phase of BP.[1]

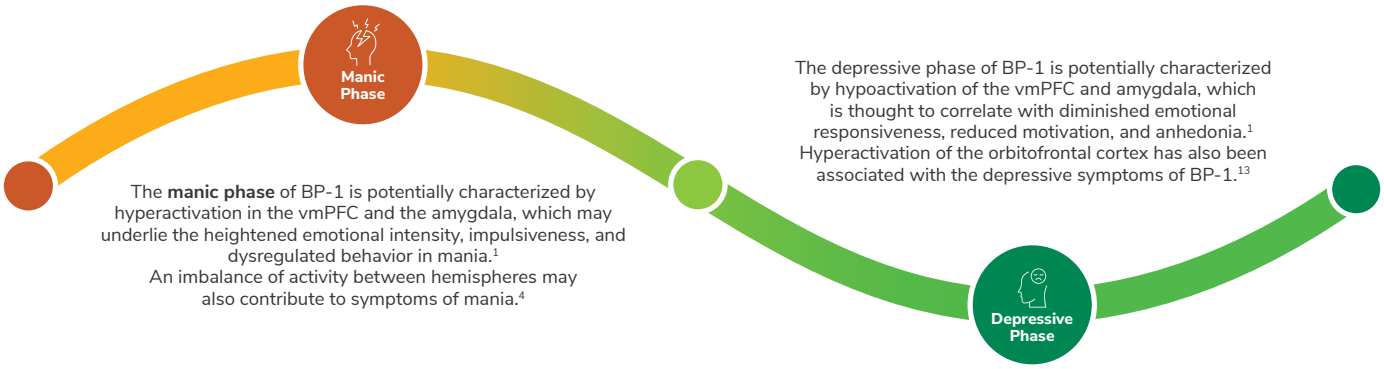


The **Salience Network** (SN) is hypothesized to play an important role in shifting attention between internal and external stimuli. The SN may be involved in cognitive and emotional regulation in BP.[1]

Figure 2. Key neural circuits thought to be affected in BP-1.[1,2] Image adapted from Bi B, et al. *Transl Psychiatry*. 2022;12(1):143. AC = auditory cortex, ACC = anterior cingulate cortex, Amy = amygdala, dACC = dorsal anterior cingulate cortex, dlPFC = dorsolateral prefrontal cortex, dmPFC = dorsomedial prefrontal cortex, Hip = hippocampus, IC = insular cortex, ITG = inferior temporal gyrus, LTC = lateral temporal cortex, mPFC = medial prefrontal cortex, OFC = orbitofrontal cortex, PCC/PCU = posterior cingulate cortex/precuneus cortex, PMC = primary medial cortex, PPC = posterior parietal cortex, SC = somatosensory cortex, SMA = supplementary motor area, TP = temporal, VC = visual cortex, vlPFC = ventrolateral prefrontal cortex, VTA/SN = ventral tegmental area/substantia nigra.

Neural Communication Pathways Implicated in BP Symptoms

Functional and structural disruptions in neural communication pathways have been implicated in altered regulation of emotions and motor activity. Abnormalities in white matter in the connections between the PFC and subcortical regions suggest that disruptions in these pathways may contribute to impaired top-down regulation of emotions and motor activity.[1]



The **manic phase** of BP-1 is potentially characterized by hyperactivation in the vmPFC and the amygdala, which may underlie the heightened emotional intensity, impulsiveness, and dysregulated behavior in mania.[1] An imbalance of activity between hemispheres may also contribute to symptoms of mania.[4]

The depressive phase of BP-1 is potentially characterized by hypoactivation of the vmPFC and amygdala, which is thought to correlate with diminished emotional responsiveness, reduced motivation, and anhedonia.[1] Hyperactivation of the orbitofrontal cortex has also been associated with the depressive symptoms of BP-1.[13]

Neuroimaging and longitudinal studies have helped to characterize the interplay of various neural networks and brain regions that may help regulate different symptom domains of BP-1.[2] Understanding the roles of neural networks and brain regions in manifesting BP-1 symptoms can help healthcare providers develop management approaches that may help address a spectrum of BP-1 symptom domains early in the treatment process.

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