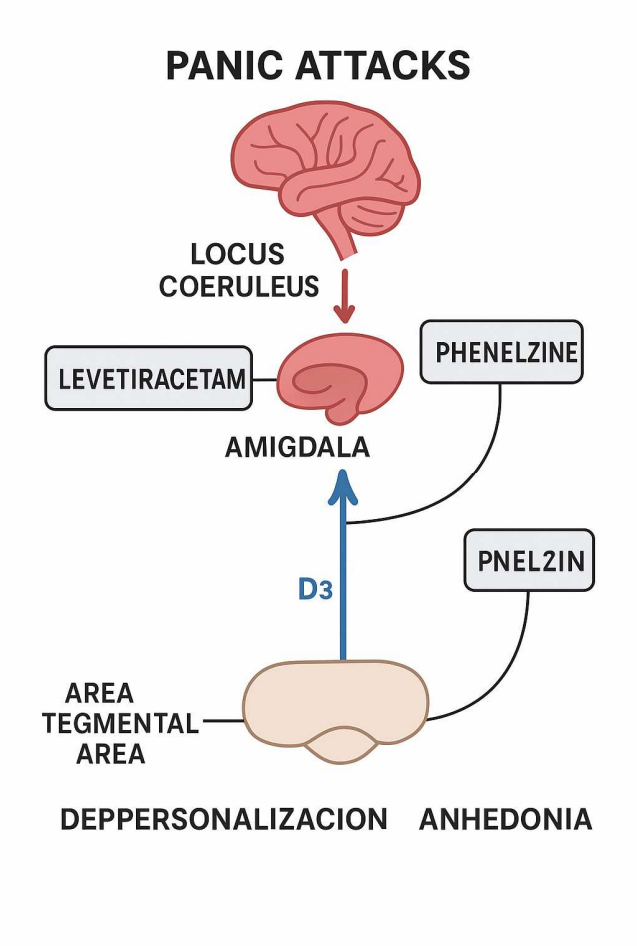
Essay: Neurobiological Regulation and Pharmacological Approach in Panic Attacks, Depersonalization, and Anhedonia



Introduction: Regulatory Systems of Anxiety and Stress

The **noradrenergic** and **dopaminergic D3** systems are two fundamental neural circuits regulating alarm responses, anxiety, and motivation.
The **locus coeruleus**, the main source of norepinephrine (NE) in the brain, acts as an activation hub that responds to both internal and external threat stimuli, sending signals to the **amygdala**, **prefrontal cortex**, **thalamus**, and **cardiorespiratory centers**.

Under normal conditions, there is a dynamic balance between **noradrenergic excitation**, which prepares the body for action, and **prefrontal cortical inhibition**, which filters excessive emotional responses from the amygdala. In predisposed individuals, however, this balance

becomes **dysregulated**, producing sudden bursts of noradrenergic activity that manifest as **panic attacks**, characterized by tachycardia, hyperventilation, tremors, and feelings of loss of control.

The Role of the Dopaminergic D3 System

The **dopaminergic system**, especially the **D3 receptors** located in the **ventral tegmental area (VTA)** and **nucleus accumbens**, regulates motivation, pleasure, and emotional engagement. Reduced D3 dopaminergic activity is linked to **anhedonia**, apathy, and emotional blunting—symptoms that frequently accompany chronic anxiety disorders.

Importantly, there is a **functional interplay between the noradrenergic and dopaminergic systems**: overactivation of the noradrenergic alarm system can suppress mesolimbic dopamine release, leading to a paradoxical state of **hyperarousal without pleasure**, i.e., a person who feels anxious, alert, but emotionally flat and unable to experience motivation or reward.

Hypersensitivity and the Kindling Process

In some patients, hyperreactivity of the locus coeruleus and amygdala becomes **self-perpetuating** through a process known as **kindling**—a progressive neuronal sensitization that maintains exaggerated responses to minor stimuli.
This mechanism may explain why certain individuals experience **spontaneous panic attacks** or persistent states of **depersonalization and derealization**, even in the absence of clear triggers.

In such cases, **anticonvulsants** like **levetiracetam** may be helpful by stabilizing neuronal excitability and reducing the synchronized over-discharge of panic-related circuits.

Pharmacological Strategies for Treatment-Resistant Cases

When patients fail to respond to conventional treatments such as **SSRIs** or standard anxiolytics, second-line strategies may aim to **normalize both noradrenergic and dopaminergic neurotransmission**.

Key pharmacological options include:

- **Levetiracetam** – stabilizes neuronal excitability and reduces limbic system reactivity.
- **D3 Dopaminergic Agonists** (e.g., pramipexole or ropinirole at low doses) – restore motivation and reward sensitivity in patients with emotional blunting or fatigue.
- **MAO Inhibitors** such as **phenelzine**, at very low doses (e.g., ¼ of a 15 mg tablet, three times daily), can promote a **physiological release of norepinephrine**, aiding in the **desensitization of adrenergic receptors** without inducing hypertensive reactions or complete enzyme blockade.

This gentle modulation helps the noradrenergic system **relearn normal regulatory dynamics** instead of remaining locked in hyperreactivity.

Practical Considerations and Combined Use

In complex clinical cases, a **combination of levetiracetam, a D3 agonist, and subtherapeutic phenelzine** may be considered under strict medical supervision.
This combined approach seeks to:

- Reduce limbic neuronal hyperexcitability,
- Normalize norepinephrine release,
- Restore dopaminergic reward tone and motivational drive.

As **PRN (as-needed)** medications, **benzodiazepines** (such as low-dose clonazepam or alprazolam) may be used to manage acute anxiety peaks while the baseline treatment gradually stabilizes the neurochemical systems.

Conclusion

Panic attacks, depersonalization, and anhedonia reflect a **coordinated dysfunction** between the brain's alarm (noradrenergic) and reward (dopaminergic) systems.
Therapeutic strategies should not only suppress anxiety but also **restore adaptive neurodynamics** that allow flexible and healthy emotional responses.

The careful, low-dose use of MAO inhibitors, anticonvulsants, and dopaminergic modulators represents a **rational, neurophysiologically grounded approach** for treatment-resistant cases—always within a framework of close monitoring and individualized patient care.