

Rethinking Narcolepsy: A Disorder Characterized by Sleep-Wake State Instability

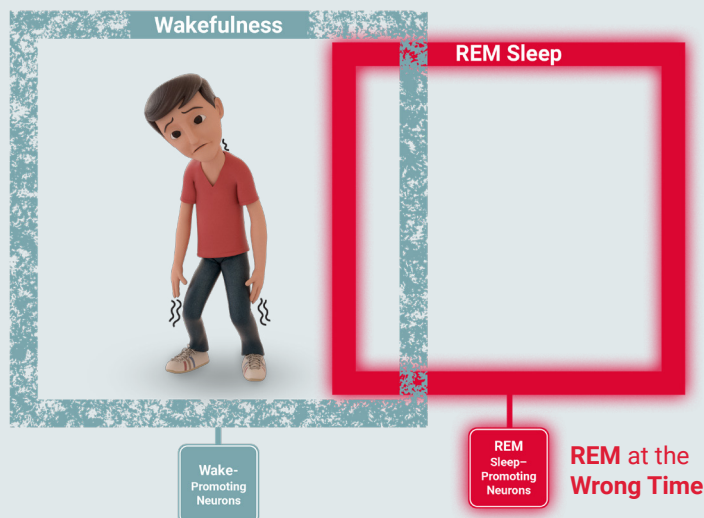
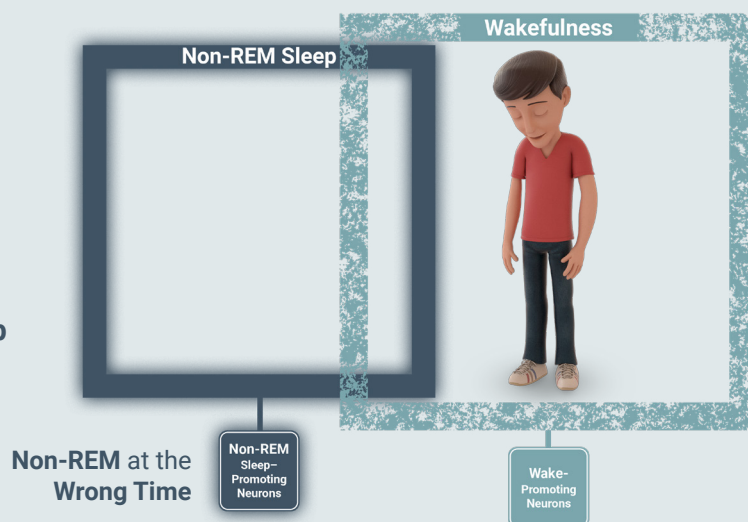
In most people with narcolepsy, loss of hypocretin/orexin neurons in the hypothalamus leads to sleep-wake state instability,¹⁻³ which manifests as:

- Frequent and unpredictable transitions between sleep-wake states^{4,5}
- Unstable boundaries between sleep-wake states, which allow elements of one state to intrude into another^{4,6}

Signs and symptoms of narcolepsy reflect the underlying sleep-wake state instability²⁻⁴

Excessive daytime sleepiness (EDS)

- Insufficient activation of wake-promoting neurons may lead to **impaired alertness and neurocognitive functioning**^{2,3,7,8}
- Insufficient inhibition of non-REM sleep-promoting neurons can allow non-REM sleep to intrude into wakefulness as **microsleep episodes or unintended lapses into sleep**^{3,9,10}

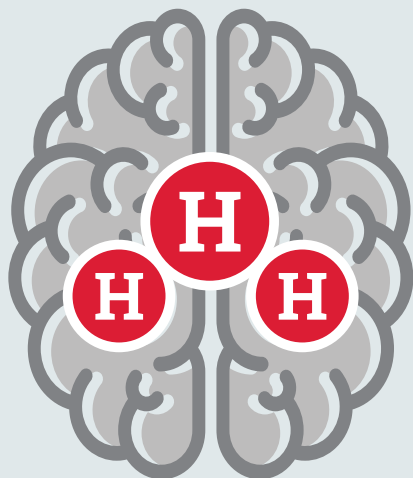


Symptoms of REM sleep dysregulation

- Insufficient inhibition and intermittent activation of REM sleep-promoting neurons during the day can lead to disordered regulation of REM sleep, which may manifest as symptoms such as **cataplexy**^{3,7}

Sleep-wake state instability in narcolepsy can manifest in a variety of ways, but the manifestations are not always obvious^{1-4,7,11}

The Underlying Neuronal Processes Behind Stable Wakefulness



3Hs of Sleep-Wake State Stability

Hypothalamus: A critical “control center” for sleep-wake state stability that contains neuronal systems that help stabilize wakefulness,^{4,12-15} including:

- **Hypocretin** neurons
- **Histamine** neurons

Histamine neurons are activated by hypocretin neurons.¹² These two neuronal systems play complementary roles in wakefulness^{2,15-17}:

Promote wakefulness^{2,12,16}

- Activate cortical neurons and subcortical wake-promoting neurons

Stabilize wakefulness^{2,12,15,16}

- Inhibit non-REM and REM sleep-promoting neurons



Access tools and resources at [KnowNarcolepsyhcp.com](https://www.knownarcolepsyhcp.com)

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US-NAR-2100105/Jun 2021