Hypothalamic Obesity

Dr. Jennifer Miller, M.D
University of Florida

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Disclosure: Consultant for Rhythm Pharmaceuticals., and is compensated for these services

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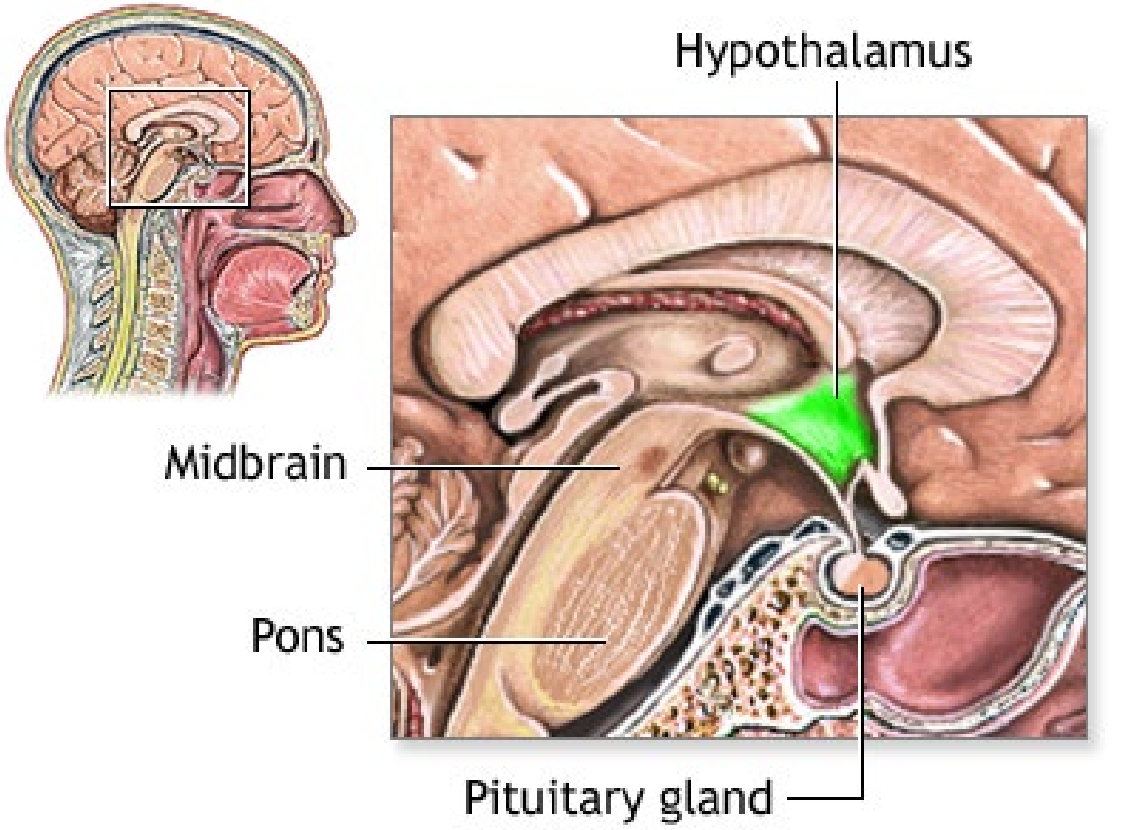
The Hypothalamus regulates multiple functions in the body

The hypothalamus plays an important role in regulating several body functions including:

- Appetite and weight
- Body temperature
- Sleep wake cycle and the Body clock
- Emotions, behavior, memory
- Childbirth
- Growth
- Sex Drive

The Hypothalamus is the central command center for hormonal regulation. In addition, the hypothalamus controls the pituitary gland a small gland that in turns controls adrenal glands, ovaries, testes and thyroid gland.



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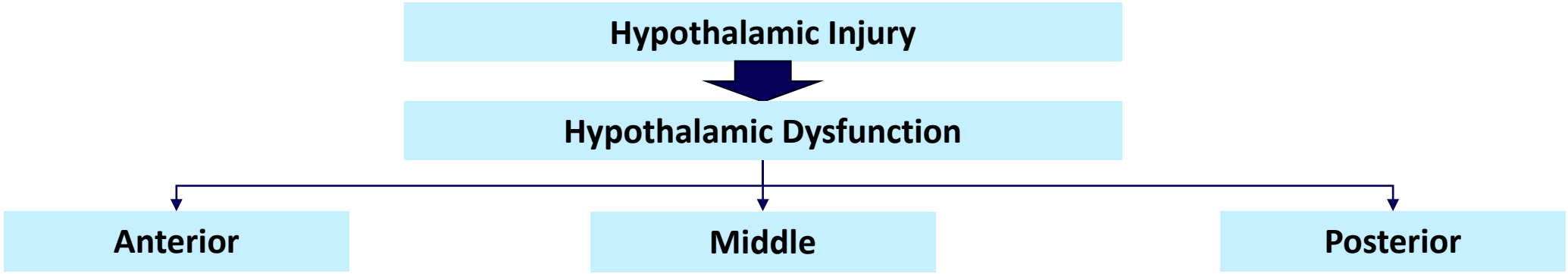
Many different and unique conditions may result from injury categorized under an umbrella term "hypothalamic dysfunction"[1]



Damage to the anterior hypothalamus disrupts sex hormone regulation, sleep, body temperature and some influence on heart failure

Damage to the middle region in the hypothalamus disrupts satiety and fullness resulting in **Hypothalamic Obesity**

Damage to the posterior region in the hypothalamus disrupts the limbic system responsible for memory, behavior and motivation, and also blood pressure regulation

1. Sanchez Jimenez JG, De Jesus O. Hypothalamic Dysfunction. [Updated 2023 Aug 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560743/

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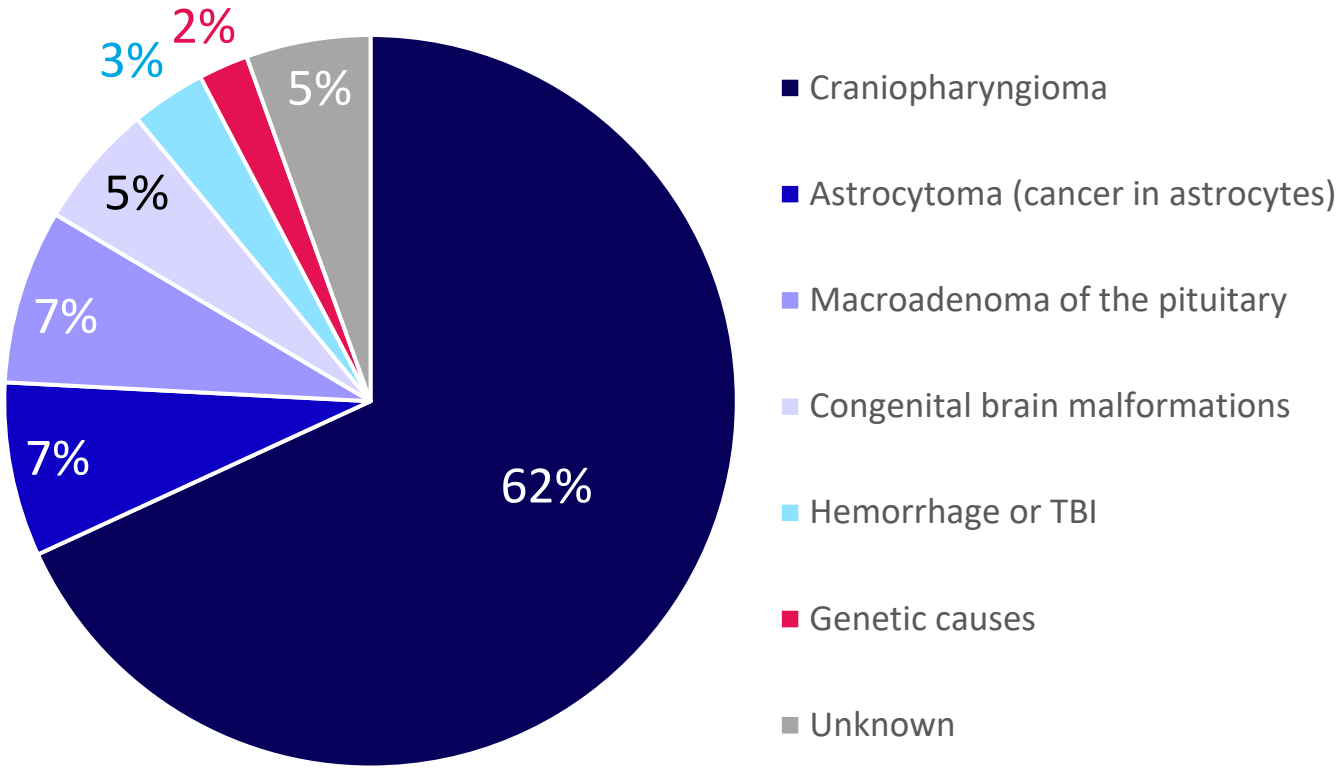
Hypothalamic Obesity is a unique condition that results from injury to the hypothalamus, and distinct from other forms of obesity[1]

- Hypothalamic Obesity (HO) is an acquired form of severe obesity, most frequently occurring following surgical or radiation treatment of brain tumors
- Most HO cases follow craniopharyngioma
  - Benign neoplasms located centrally within the brain
  - Frequently impact hypothalamus, pituitary gland, and optic nerve
  - Treatment of the tumor includes gross total resection, proton beam therapy, and hormone replacement therapy to compensate for pituitary gland damage
- Approximately 50% of patients who receive treatment for craniopharyngioma develop HO



Rose SR, Horne VE, Bingham N, Jenkins T, Black J, Inge T. Hypothalamic Obesity: 4 Years of the International Registry of Hypothalamic Obesity Disorders. Obesity (Silver Spring). 2018 Nov;26(11):1727-1732. doi: 10.1002/oby.22315. Epub 2018 Oct 8. PMID: 30296362; PMCID: PMC6202209.

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U.S. Prevalence of Hypothalamic Obesity is estimated at 5-10,000 patients; with an additional ~500 cases diagnosed each year[1]

2,500–7,500	>1,000	>1,500
HO related to craniopharyngioma	HO related to astrocytoma (cancer of astrocytes)	HO related to other tumor types

Estimate of tumor incidence and prevalence anticipated to be similar across other countries

HO, hypothalamic obesity.

[a]To estimate the number of patients with incident and prevalent craniopharyngioma and astrocytoma with obesity, Rhythm analyzed the literature and used the number of new cases each year in the United States, overall survival rates after a diagnosis of each brain tumor type, and obesity rates among those patients at diagnosis or after diagnosis.

1. Rhythm Pharmaceuticals, Inc. Interim results from phase 2 clinical trial evaluating setmelanotide in hypothalamic obesity. Presented July 12, 2022; Virtual. https://ir.rhythmtx.com/static-files/86283e4f-3493-4c62-af27-a47ca6eab048. Accessed August 9, 2022

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Clinical Manifestations of Hypothalamic Obesity Include Decreased Energy Expenditure and Hyperphagia

Decreased Energy Expenditure	Hyperphagia
Decreased sympathetic activity (ie, heart rate, blood pressure, body temperature) can result in overall reduced metabolic activity and decreased physical activity	**Substantial feelings of hunger, which, in combination with impulse disorders, can result in food cravings and overeating** *Hyperphagia is not always reported with HO; however, hypothalamic injury may lead to dysregulation of hunger, satiety, and, consequently, hyperphagia*[1,3]

HO, hypothalamic obesity.

1. Van Iersel et al. *Endocr Rev.* 2019;40:193-235. **2.** Rose et al. *Obesity (Silver Spring).* 2018;26:1727-1732. **3.** Dimitri. *Front Endocrinol (Lausanne).* 2022;13:846880.

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Pharmacologic Treatment Options

- There is a lack of clear treatment algorithms for HO, and there are no therapies specifically indicated for this unique type of obesity[1]
- Many pharmacologic treatments that are indicated for general weight loss (e.g. GLP-1 products) have been explored for use in patients with HO[1,2]
- A range of case studies, observational studies, as well as a limited number of randomized control trials have assessed the impact of pharmacotherapies on HO[1,2]
- There are currently several treatments under investigation for HO

59%

of patients reported using pharmacotherapy (and ~26% reported multidrug therapy)[3]

In part because of the unique pathophysiology of HO compared with general forms of obesity, conventional pharmacologic approaches have shown limited to no benefit in patients with HO, and there are currently no FDA-approved treatments available for these patients[1,3]

HO, hypothalamic obesity.

1. Singhal et al. *Curr Opin Endocrinol Diabetes Obes.* 2021;28:55-63. **2.** Müller et al. *Endocrinol Metab Clin North Am*. 2020;49(3):533-552. **3.** Rose et al. *Obesity (Silver Spring).* 2018;26:1727-1732.

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Summary

Hypothalamic obesity (HO) is a specific condition, distinct from other types of obesity as well as from other conditions that may relate to dysfunction of the hypothalamus. Thus, a new code is needed to properly identify, diagnose and track for patients with HO and the clinical interventions used to treat and manage them.

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