narcolepsy

nerd alert

# SCIENCE OF NARCOLEPSY

Created by:

projectsleep

narcolepsy nerd alert

# TOOLKIT INDEX

# WELCOME!

We are so glad you are here. This toolkit is designed for people living with narcolepsy and their loved ones to offer new tools, tips, and perspectives on navigating narcolepsy. Project Sleep created this toolkit as part of the **Narcolepsy Nerd Alert** series.

**Narcolepsy Nerd Alert** is an educational series diving deeper into specific topics relevant to narcolepsy. Each month, Project Sleep broadcasts a live event via Facebook, hosted by Julie Flygare, JD, Project Sleep's President & CEO.

After each live broadcast, we create a corresponding toolkit (like this one!) to capture our collective knowledge to help others down the road. Quotes featured throughout the toolkit are from panelists and audience members who joined us for the live broadcast.

# PLEASE NOTE

The **Narcolepsy Nerd Alert** series is intended for educational and awareness purposes and is not a substitute for medical attention. If anything in this toolkit sparks questions for you about your medical management, please bring those questions to your sleep doctor or narcolepsy specialist.

# MEET OUR GUEST

**Dr. Thomas Scammell, MD** received his Doctor of Medicine degree from the University of Massachusetts Medical School, where he trained in internal medicine. He also completed a residency in Neurology at the University of California, San Francisco, and a fellowship in Sleep Medicine at Beth Israel Deaconess Medical Center.

Dr. Scammell is a Professor in Neurology at Harvard Medical School, Beth Israel Deaconess Medical Center, and Boston Children's Hospital. He serves as an ad hoc reviewer for New England Journal of Medicine, Annals of Neurology, Nature, Cell, and Neuron, and was a Deputy Editor of SLEEP. He was a member of the International Classification of Sleep Disorders Task Force, the Sleep Research Society Board of Directors and the APSS Program Committee.

The author of over 150 journal articles and chapters, Dr. Scammell has lectured both nationally and internationally on narcolepsy and the neurobiology of sleep and wakefulness. His current research interests include identifying how loss of orexin signaling results in sleepiness and cataplexy, development of new medications for narcolepsy, interactions of sleep and pain, and sleep disorders in Prader-Willi Syndrome.


## MEET THE HOST

**Julie Flygare, JD,** currently serves as President & CEO of Project Sleep. She was diagnosed with narcolepsy with cataplexy in 2007 while in law school. Julie is an internationally recognized patient-perspective leader, an accomplished advocate, and the award-winning author of *Wide Awake and Dreaming: A Memoir of Narcolepsy.*

# THE SCIENCE OF NARCOLEPSY

## Science nerds -- this one's for you!

On August 25, 2021, special guest Dr. Thomas Scammell, MD, Professor of Neurology at Harvard Medical School, joined host Julie Flygare to dive into the neurobiology of narcolepsy.

Narcolepsy is a *neurological condition* -- so what's actually happening in the brain and nervous system? Scientific advancements in the last two decades have greatly improved our understanding of sleep and wakefulness, and led to new treatments for narcolepsy and other sleep disorders. This toolkit presents research that informs our current understanding of narcolepsy along with Dr. Scammell's answers to - in his words - some "very good questions" from the community.

- Watch the Science of Narcolepsy Video
- Learn more about the Narcolepsy Nerd Alert Series

**Stumped on a term?**
**See the glossary at the end of the toolkit.**

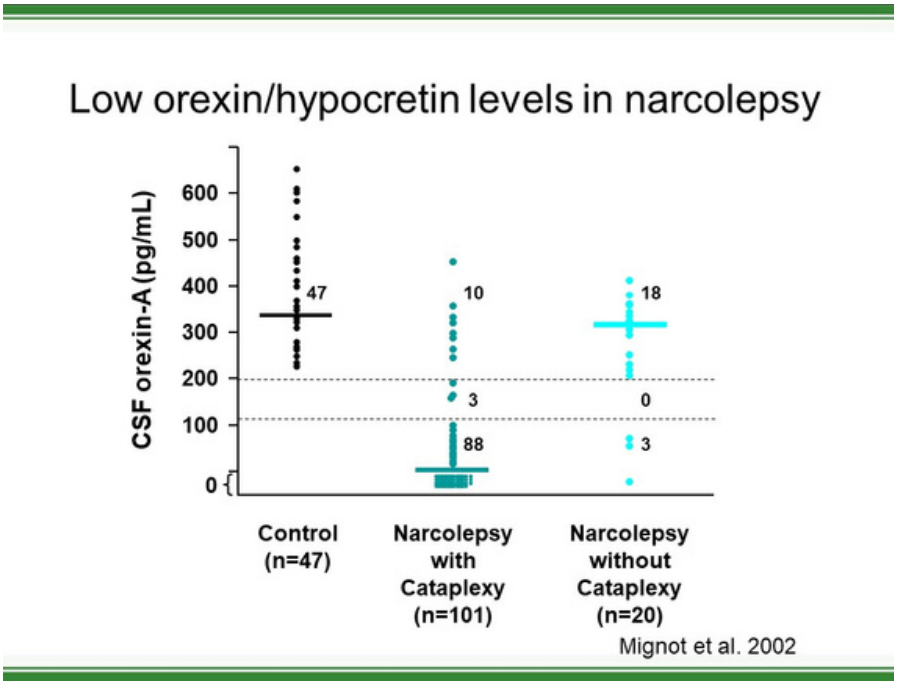
### WHAT QUESTIONS DO YOU HAVE ABOUT NARCOLEPSY?

# BACKGROUND

What is the neurological difference between people who have narcolepsy with cataplexy, narcolepsy without cataplexy, and people who don't have narcolepsy?

- While narcolepsy was identified in 1870, for a long time the underlying cause was unknown.
- In the late 1990s, researchers found that people who have type 1 narcolepsy, or narcolepsy with cataplexy, lack specific neurotransmitters called **orexins**, which are also known as **hypocretins.**
- Orexins are **necessary for the regulation of the sleep-wake cycle.**

The figure below is from a study led by Dr. Emmanuel Mignot showing that **type 1 narcolepsy is caused by a lack of orexins.**




People with type 1 narcolepsy had significantly reduced orexin levels, about 95% less in their cerebrospinal fluid (CSF) compared to people who do not have narcolepsy. People with type 2 narcolepsy, which is narcolepsy without cataplexy, had comparable levels of orexins to those without narcolepsy. More research is needed to better understand type 2 narcolepsy.

narcolepsy nerd alert

# DEVELOPMENT OF NARCOLEPSY

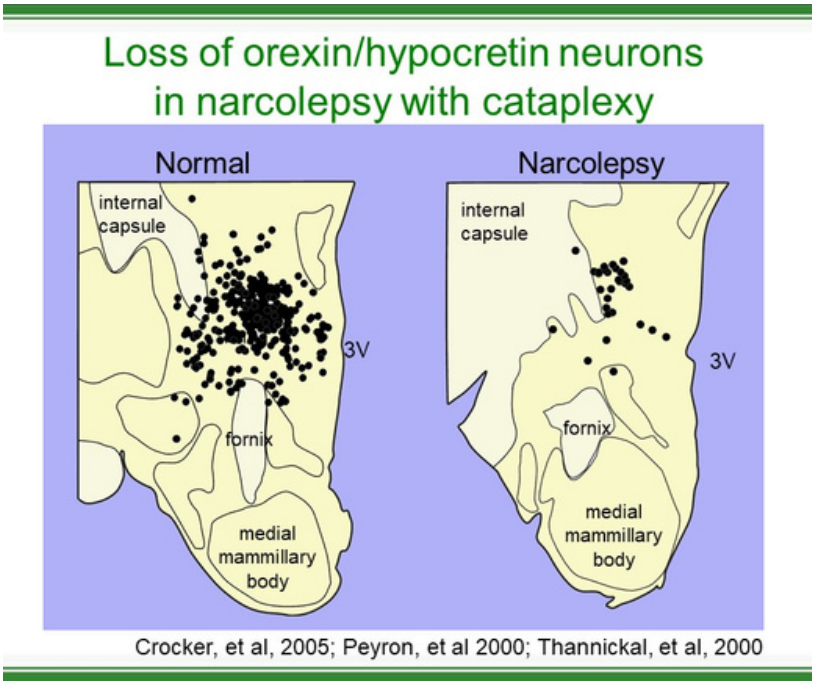
***Who can develop narcolepsy?***

The likelihood of developing narcolepsy depends on three main factors:

1. Some people are **genetically predisposed** to develop type 1 narcolepsy. (Genetic factors are discussed further in a later section.)
2. People in a certain **age range** – late adolescence to early adulthood – are more likely to develop narcolepsy.
3. Usually an **immune trigger** precedes narcolepsy symptoms. (Immune triggers are discussed further in a later section.)

***Where do orexins come from?***

Orexins are produced by a group of neurons located in the hypothalamus, a part of the brain that helps **regulate sleep and circadian rhythms**. The figure below shows a cross section of the hypothalamus, with the location of the orexin-producing neurons indicated by black dots.




Low levels of orexins observed in type 1 narcolepsy are due to 90-95% loss of the orexin-producing neurons in the brain. Dr. Scammell says, "**Loss of orexin-producing neurons is the major cause of type 1 narcolepsy.**"

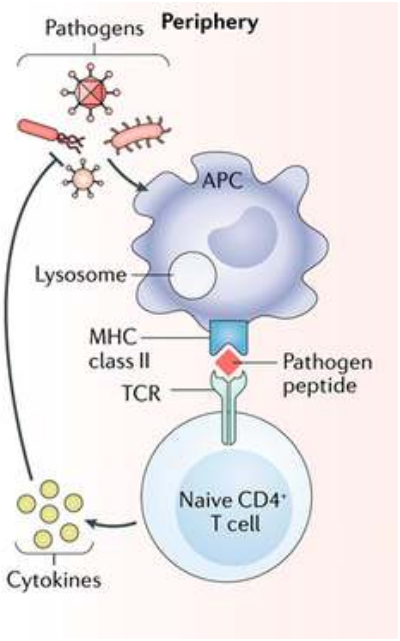
There is limited research on these neurons in type 2 narcolepsy.

# DEVELOPMENT OF NARCOLEPSY

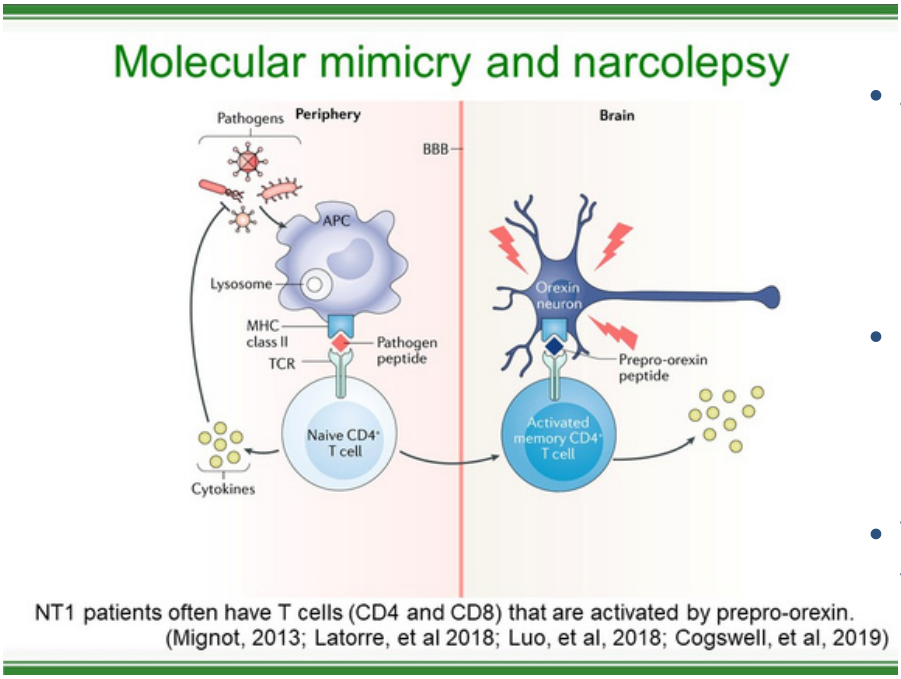
***Why do some brains stop making orexins?***

The loss of orexin-producing neurons is due to a process called *molecular mimicry*. Essentially, **the body's natural immune response mistakenly kills the orexin-producing neurons**. So how does this happen?

- Every day your body fights off pathogens, which are bacteria and viruses.
- When antigen presenting cells (APC) find a pathogen, they consume it and chop it up into tiny pieces, called pathogen peptides.
- The APC then presents the pathogen peptides to immune cells called T cells.
- The T cells are activated to make chemicals called cytokines that help other parts of the immune system recognize and fight the pathogen.




**This process usually protects us from infections, so how can it lead to narcolepsy?**



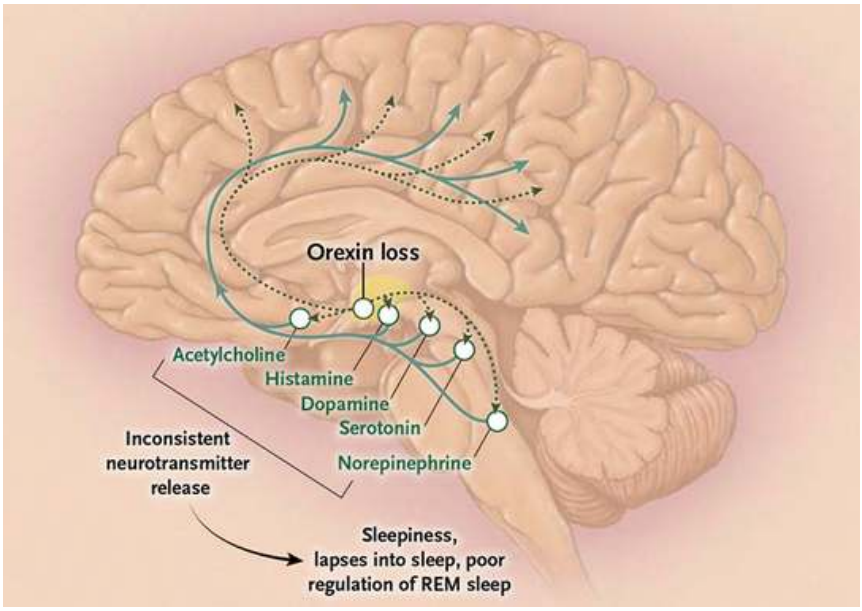

NT1 patients often have T cells (CD4 and CD8) that are activated by prepro-orexin.
(Mignot, 2013; Latorre, et al 2018; Luo, et al, 2018; Cogswell, et al, 2019)

- An infection such as strep can sometimes weaken the blood-brain barrier, allowing T cells to cross and enter the brain.
- Orexin neurons contain peptides which mimic the pathogen peptides the T cells are "looking for."
- The T cells mistakenly kill the orexin neurons.

# NEUROBIOLOGY OF SLEEPINESS

***How does loss of orexin neurons lead to sleepiness?***
New research presented by Dr. Scammell shows that **loss of orexins impairs the functioning of other wake-promoting systems.**

The figure below is a cross-section of the brain, with the cortex at the top and the brainstem at the bottom. Shaded in yellow in the middle is the hypothalamus. This is where the **orexin neurons** are located.




For people without narcolepsy, the orexin neurons send **strong signals** to turn on other parts of the brain that promote wakefulness by releasing neurotransmitters such as acetylcholine, histamine, dopamine, serotonin, and norepinephrine.

Without orexins, as in type 1 narcolepsy, these other regions of the brain are not consistently getting the signal to release the neurotransmitters that would keep you awake. The result is that people with narcolepsy feel sleepy and easily lapse into sleep. Dr. Scammell adds, "if you don't have enough, for instance, norepinephrine or serotonin, your REM sleep is going to get weird too."

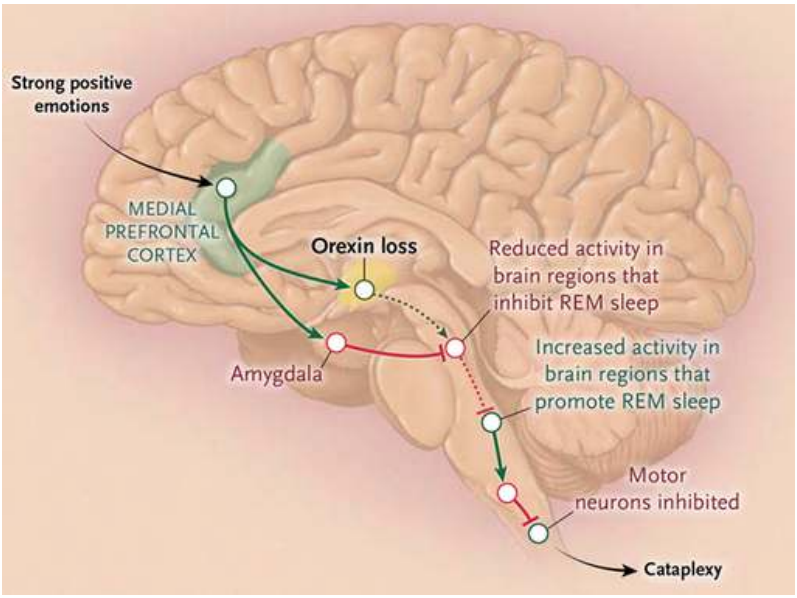
> The sleepiness of narcolepsy is fundamentally about poor maintenance of wakefulness. The normal, consistent alertness that most people have just doesn't work well in narcolepsy.
>
> - Dr. Scammell

narcolepsy nerd alert

# NEUROBIOLOGY OF CATAPLEXY

***How does a strong emotional trigger lead to muscle weakness?***
This is a question Dr. Scammell's lab and others have been trying to answer using mouse models of narcolepsy.

- First, you **perceive** something funny, surprising, etc., which occurs in the *medial prefrontal cortex* area of your brain.
- Normally, the medial prefrontal cortex would **excite orexin neurons** in the hypothalamus (which helps regulate sleep) and other neurons in the **amygdala**, an emotion regulating area.
- The amygdala **reduces** brain activity that suppresses REM sleep. Normally, orexins **increase** activity that suppresses REM sleep, so the two would **balance** out.




> We're starting to put together the pathways, and this picture gives you an idea of what we're thinking right now.
> - Dr. Scammell

- **Without orexins, the amygdala is unopposed** and turns off the brain regions that should be "putting the brakes" on REM sleep.
- This allows for **increased activity** in brain regions that promote REM sleep, especially the **paralysis of REM sleep.**
- Ultimately, this **inhibits the motor neurons that control muscles,** and cataplexy occurs.

narcolepsy nerd alert

# GENETIC FACTORS

What do your genes have to do with narcolepsy?

> We have known since the 1980s that narcolepsy is strongly linked to a particular gene that goes by this awkward name of HLA-DBQ1*06:02.
>
> - Dr. Scammell

Everyone has a section of their DNA called the HLA-DBQ1 gene, which is involved in the body's immune response. Many versions of this gene exist. Researchers identified one specific version of the gene, called *06:02, which is found in the DNA of most people with narcolepsy.

- Over 90% of people with type 1 narcolepsy carry the *06:02 gene.
- Over 50% of people with type 2 narcolepsy carry the gene.
- 10-25% of the general population, i.e. people without narcolepsy, carry the gene too.



> Having this gene alone doesn't make you develop narcolepsy, but it seems to be a fairly necessary prerequisite. Very few people who have type 1 narcolepsy lack *06:02.
>
> - Dr. Scammell

***Would an at-home genetic test tell me if I have the gene for narcolepsy?***
Probably not. Your sleep specialist can order a test for it, but this is not common because having the *06:02 gene doesn't necessarily mean you have narcolepsy. However, Dr. Scammell says it can be a useful tool for a doctor to increase or decrease confidence in a narcolepsy diagnosis after a 24-hour sleep study.

# ENVIRONMENTAL FACTORS

## What can trigger the immune response that leads to narcolepsy?

If a person is genetically predisposed to develop narcolepsy, an immune trigger often precedes the onset of narcolepsy symptoms. Dr. Scammell explained that the immune response leading to the loss of orexin neurons can even be triggered by "very mundane infections such as strep."

Not everyone with narcolepsy can identify a specific infection that may have brought on their symptoms, especially as diagnosis often does not come until years after symptom onset.

> There is a kind of seasonality to narcolepsy onset. In China where there is pretty good tracking of cases, it seems that the onset of narcolepsy is more common from March through June. This suggests that if there's a lag of a month or two, maybe some winter infection was a triggering event.
>
> - Dr. Scammell

***Can emotional trauma, PTSD, or stress trigger the onset of narcolepsy in people who are genetically predisposed?***

Dr. Scammell says, "While it's a interesting question -- whether or not a period of stressful circumstances, trauma, or sleep deprivation can trigger narcolepsy -- I'm not aware of any evidence connecting the dots."

> I don't encourage people to stress too much about developing narcolepsy or what caused them to develop narcolepsy. You have to live your life and not worry about the triggering things.
>
> - Dr. Scammell

# RESOURCES

Here are some of our favorite resources. We look forward to hearing what our fellow #NarcolepsyNerds find most useful for learning about the science of narcolepsy!

## PATIENT ORGANIZATIONS

- Major US Organizations:
  - Hypersomnia Foundation
  - Narcolepsy Network
  - Project Sleep
  - Wake Up Narcolepsy
- International Organizations:
  - Listed on Project Sleep's World Narcolepsy Day webpage

## REFERENCES


Cogswell, A. C., Maski, K., Scammell, T. E., Tucker, D., Orban, Z. S., & Koralnik, I. J. (2019). Children with narcolepsy type 1 have increased T-cell responses to orexins. Annals of Clinical and Translational Neurology, 6(12), 2566–2572.

Crocker, A., España, R. A., Papadopoulou, M., Saper, C. B., Faraco, J., Sakurai, T., Honda, M., Mignot, E., & Scammell, T. E. (2005). Concomitant loss of dynorphin, NARP, and orexin in narcolepsy. Neurology, 65(8), 1184–1188.

Latorre, D., Kallweit, U., Armentani, E., Foglierini, M., Mele, F., Cassotta, A., Jovic, S., Jarrossay, D., Mathis, J., Zellini, F., Becher, B., Lanzavecchia, A., Khatami, R., Manconi, M., Tafti, M., Bassetti, C. L., & Sallusto, F. (2018). T cells in patients with narcolepsy target self-antigens of hypocretin neurons. Nature, 562(7725), 63–68.

Luo, G., Ambati, A., Lin, L., Bonvalet, M., Partinen, M., Ji, X., Maecker, H. T., & Mignot, E. J.-M. (2018). Autoimmunity to hypocretin and molecular mimicry to flu in type 1 narcolepsy. Proceedings of the National Academy of Sciences, 115(52), E12323–E12332.

# RESOURCES

## REFERENCES


Mahlios, J., De la Herrán-Arita, A. K., & Mignot, E. (2013). The autoimmune basis of narcolepsy. Current Opinion in Neurobiology, 23(5), 767–773.

Mahoney, C. E., Cogswell, A., Koralnik, I. J., & Scammell, T. E. (2019). The neurobiological basis of narcolepsy. Nature Reviews Neuroscience, 20(2), 83–93.

Mignot, E., Lammers, G. J., Ripley, B., Okun, M., Nevsimalova, S., Overeem, S., Vankova, J., Black, J., Harsh, J., Bassetti, C., Schrader, H., & Nishino, S. (2002). The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Archives of Neurology, 59(10), 1553–1562.

Peyron, C., Faraco, J., Rogers, W., Ripley, B., Overeem, S., Charnay, Y., Nevsimalova, S., Aldrich, M., Reynolds, D., Albin, R., Li, R., Hungs, M., Pedrazzoli, M., Padigaru, M., Kucherlapati, M., Fan, J., Maki, R., Lammers, G. J., Bouras, C., … Mignot, E. (2000). A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nature Medicine, 6(9), 991–997.

Thannickal, T. C., Moore, R. Y., Nienhuis, R., Ramanathan, L., Gulyani, S., Aldrich, M., Cornford, M., & Siegel, J. M. (2000). Reduced number of hypocretin neurons in human narcolepsy. Neuron, 27(3), 469–474. https://doi.org/10.1016/S0896-6273(00)00058-1

narcolepsy nerd alert

# GLOSSARY

**amygdala -** an area of the brain that is involved in regulating emotions.

**antigen presenting cell (APC)** - a type of immune cell that boosts immune responses by showing antigens on its surface to other cells of the immune system.

**cataplexy** - striking, sudden episodes of muscle weakness usually triggered by strong emotions such as laughter, exhilaration, surprise, or anger. The severity may vary from a slackening of the jaw or buckling of the knees to falling down. The duration may be for a few seconds to several minutes and the person remains fully conscious (even if unable to speak) during the episode.

**cerebrospinal fluid (CSF)** - a watery fluid that flows around the hollow spaces of the brain and spinal cord.

**cytokines** - molecules used by the immune system to transmit messages between cells.

**genetic marker** - a gene or short section of DNA that can be detected and often is used to identify individuals who may develop a certain condition.

**gene** - a section of DNA that holds the "instructions" or code for cells to make a certain molecule. Often, many different versions of one gene (alleles) exist, and which version a person has is inherited from their parents.

**genetic predisposition** - an increased likelihood of developing a certain condition based on inherited genes.

**hypocretins** - neurotransmitters involved in the regulation of sleep and wakefulness. Also called **orexins**.

**hypothalamus** - an area of the brain where neurotransmitters are released. One important function of the hypothalamus is to maintain a constant, stable state.

**immune trigger** - an event which activates the body's defense against infections.

**molecular mimicry** - when the body's natural defense against infection mistakenly identifies its own tissues as a threat.

**neurological** - relating to the brain as well as the nerves found throughout the body and spinal cord.

**neurons** - the cells that make up the brain and nervous system. also called nerve cells.

.

narcolepsy nerd alert

# GLOSSARY

**neurotransmitters** - molecules used by the nervous system to transmit messages between cells. also called chemical messengers or hormones.

**orexins** - neurotransmitters involved in the regulation of sleep and wakefulness. also called hypocretins.

**orexin neurons** - a group of cells in the brain which produce and release the neurotransmitter orexin. also called orexin-producing neurons, orexin/hypocretin neurons.

**pathogen** - viruses and bacteria which could cause infection.

**pathogen peptide** - a small part of a viral or bacterial cell (pathogen) which has been chopped up (processed) by an antigen presenting cell.

**peptide -** a molecule consisting of 2 or more amino acids.

**strep** - strep throat is an infection in the throat and tonsils caused by bacteria called group A Streptococcus. Some narcolepsy cases have been linked to strep infection.

**T cell** - a type of cell that helps the immune system by releasing molecules which change the activity of other immune cells.

**06:02** - the version of the HLA-DBQ1 gene that is carried by most people with Type 1 narcolepsy.


# THANK YOU!

We are so grateful that you took the time to check out this toolkit!

**Project Sleep** is a 501(c)(3) nonprofit organization dedicated to raising awareness about sleep health and sleep disorders.

More resources at: www.project-sleep.com

projectsleep