

Through a Broader Lens: Looking at Non-Motor Symptoms in HD



Sleep deficits precede motor problems in HD

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Common depictions of HD emphasizing only its movement symptoms paint an incomplete picture of the real disease. HD causes both motor and non-motor symptoms that, together, affect the entire body. Now, scientists are using a broader lens to explore this full set of HD symptoms and determine how symptoms might be related in the disease.

Zooming Out

Although television shows and movies often depict Huntington's disease (HD) as a straightforward motor disorder, anyone in the Huntington's community knows that this image is a huge oversimplification. Understanding HD requires zooming out and viewing the disease through a much broader lens. In reality, HD is a systemic disease that affects many different parts of the body and aspects of life, and its non-motor symptoms can be just as devastating as their more infamous movement counterparts.

Our growing understanding of HD as a systemic disease brings new questions to the floor. What are the *very first* signs and symptoms of HD? How are different symptoms related? Do early HD symptoms affect later ones?

In this post, we'll talk about new research beginning to answer these questions.

Symptom Close-Up

This new research centers on HD symptoms disrupting two important aspects of health: sleep and body weight.

Let's start with sleep. You can tell how crucial sleep is for us humans by how much we do it: the average person spends more time sleeping than working, watching television, cooking, and cleaning *combined*.

People with HD, however, suffer sleep disruptions beginning early in the disease that affect both the quantity and quality of their sleep. As we've discussed previously, individuals



Rather than being a simple motor disease, HD is a systemic disease that affects many different parts of the body and aspects of life.

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with HD wake more often and sleep less soundly than people without the disease. We don't know exactly why these sleep disruptions happen, but out-of-whack levels of a hormone called melatonin may be involved (read more about melatonin in HD here).

This sleep loss is important, because—even for healthy people—not getting enough shut eye is associated with a whole slew of physical and mental health issues. Heart attack, weight gain, cognitive problems—the risk for all of these, and many other health problems besides, grows when our sleep is disturbed.

People with HD also often experience progressive weight loss and low body weight during the course of their disease. Scientists are still investigating the cause of these symptoms, but we know already that it isn't just that people with HD don't eat enough. Instead, these symptoms may be a consequence of changes in energy balance and/or metabolism. Just like with sleep, though, these symptoms predispose people with HD to additional health concerns.

Based on these links, some scientists wonder if sleep and metabolism problems could exacerbate, or even trigger, other HD symptoms. For this idea to be true, these problems would need to pop up very early in the disease *before* other symptoms arise. However, we don't know if this is the case (or not) because no one has ever pinpointed when (and if) sleep and metabolism problems actually begin in HD.

Framing the Question

To answer this question, a team of scientists at the University of Cambridge led by Dr Roger Barker designed a research study examining sleep and metabolism in HD.

In their study, Barker's team gathered three groups of subjects: people without HD, people with pre-symptomatic HD (who had no motor symptoms yet), and people with early HD (who had mild motor symptoms). Because these subjects were all at different stages of health or disease, they gave the scientists an easy way to see what symptoms look like as HD progresses.

The scientists studied these subjects very thoroughly in the laboratory and in "real life" via questionnaires, movement and brain wave monitoring, blood tests, and measures of energy use. Being so thorough gave them confidence that whatever they observed would reflect what really happens in the disease.

A Picture Develops

This research revealed an interesting picture of sleep and metabolism in HD.



To frame the question of when sleep and metabolism problems might arise in HD, a team of scientists examined both at different stages of health and disease.

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For sleep, deficits began during pre-symptomatic disease and were evident long before motor symptom onset. Similar to what happens in the later disease, these deficits primarily disrupted sleep continuity: people with pre-symptomatic HD woke up more often, spent more time awake in the middle of the night, and slept less soundly than their non-HD counterparts. These problems were progressive and worsened during early HD.

In contrast, **similar deficits in metabolism *did not* occur ahead of motor symptom onset**. In fact, the scientists didn't observe *any* convincing metabolic differences between healthy volunteers and people with either pre-symptomatic or early HD. This finding was surprising, given the progressive weight loss/low body weight associated with HD, but it has already been confirmed by a second, completely independent study headed by Dr Thomas Warner at University College London.

Increasing the Resolution

Together, these results give us a higher-resolution image of non-motor symptoms in HD.

First, they show us that sleep disruptions are among HD's first symptoms. Sleep disruptions begin before motor symptoms, just when early deficits in judgment, memory, and other cognitive skills are beginning to show up (more on this later).

Second, they highlight a little piece of the brain called the hypothalamus in HD. The hypothalamus is only about the size of an almond, but it plays an important role in regulating our states of sleep and wakefulness. If changes in this tiny part of the brain are responsible for sleep problems in HD, then these would be among the earliest brain changes to occur in the disease. Understanding these early changes could give us a good foundation for understanding the more widespread brain changes that occur during later HD.

Third, because the sleep deficits were *easily measurable*, they bring to the floor a potential new biomarker of HD onset or progression. Biomarkers are tests that measure or predict the progression of diseases like HD, and they're important because they let us objectively describe the disease. A biomarker focused on some aspect of sleep that could be non-invasively monitored over time would be a valuable tool in clinical trials and could eventually help to predict when a given individual would develop motor symptoms.

Finally, that this study did not find obvious deficits in metabolism emphasizes how important it is to **test** our ideas about what's happening in HD - because sometimes we're wrong. An explanation for low body weight based on altered metabolism was an attractive idea, but the new data simply don't support it. Finding this out now is really good, because now we can move forward as we look for another, better explanation for body weight symptoms in HD.

A Flash of Speculation



Because not getting enough sleep wreaks havoc on cognitive skills, it is tempting to imagine a

One of the most intriguing findings from this research is that sleep deficits arise at the same time as early deficits in judgment, memory, and other cognitive skills during pre-symptomatic HD.

scenario in which early sleep deficits cause cognitive deficits in HD.

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This finding is intriguing because we know that insufficient sleep wreaks havoc on the brain. For example, the moderate sleep deprivation caused by just 17 hours of wakefulness affects performance as much as a 0.05% blood alcohol level, and several major historical disasters (eg, the 1989 Exxon Valdez oil spill off Alaska, the Challenger space shuttle disaster, and the Chernobyl nuclear accident) have been attributed in part to human cognitive errors caused by lack of sleep. Thus, it is reasonable to speculate that early changes in sleep could directly contribute to cognitive changes in the early stages of HD.

Though a link between cognitive problems and lack of sleep in HD is an interesting idea, we have to be careful about assuming that it's true. To understand why, consider the following analogy. Imagine that you are studying crime in New York City and discover a relationship between petty crime and ice cream sales: whenever ice cream sales are booming, petty crime increases; whenever ice cream sales slump, petty crime decreases.

Given the clear relationship between these two events, would you claim that ice cream sales *cause* crime? Probably not. Instead, you'd come to the much more reasonable conclusion that **some other factor** affects both (for example, temperature - during the summer, rising temperatures could lead to more ice cream sales and more crime; during the winter, it'd be too cold for either).

We use the *exact same reasoning* when we talk about the relationship between sleep and cognitive deficits in HD. Even though these symptoms arise at the same time and track with one another, **we don't have enough information yet** to know whether one symptom causes the other or if both are the result of some other factor in the disease. Teasing apart these possibilities is an important question that will require more research.

The Big Picture

We think that this is a solid research study showing that sleep deficits precede overt motor problems in HD (but that metabolism deficits don't), and we're eager to see this work applied to developing biomarkers and understanding early brain changes. Further, we're intrigued by the possibility of a mechanistic link between sleep and cognition and await further work toward this end.

Overall, this study is also a really good reminder of HD's complexity. Broadening our lens to understand this complexity and identify both when symptoms arise and how they interact is crucial for bringing the disease, and effective treatments, into focus. Finally, while we wait for effective therapies for HD, we have pretty good medications to help with sleep, which we encourage HD patients to speak with their physician about!

The authors have no conflicts of interest to declare. For more information about our disclosure policy see our FAQ...

Glossary

hypothalamus A tiny brain region with important roles in controlling the body's hormones and metabolism

metabolism The process of cells taking in nutrients and turning them into energy and building blocks to build and repair cells.

biomarker a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.

Melatonin a hormone produced by the pineal gland, important for regulating sleep

hormone Chemical messengers, produced by glands and released into the blood, that alter how other parts of the body behave

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