



A Few Bad Seeds: Using Brain Fluid to Grow Clumps in Brain Cells

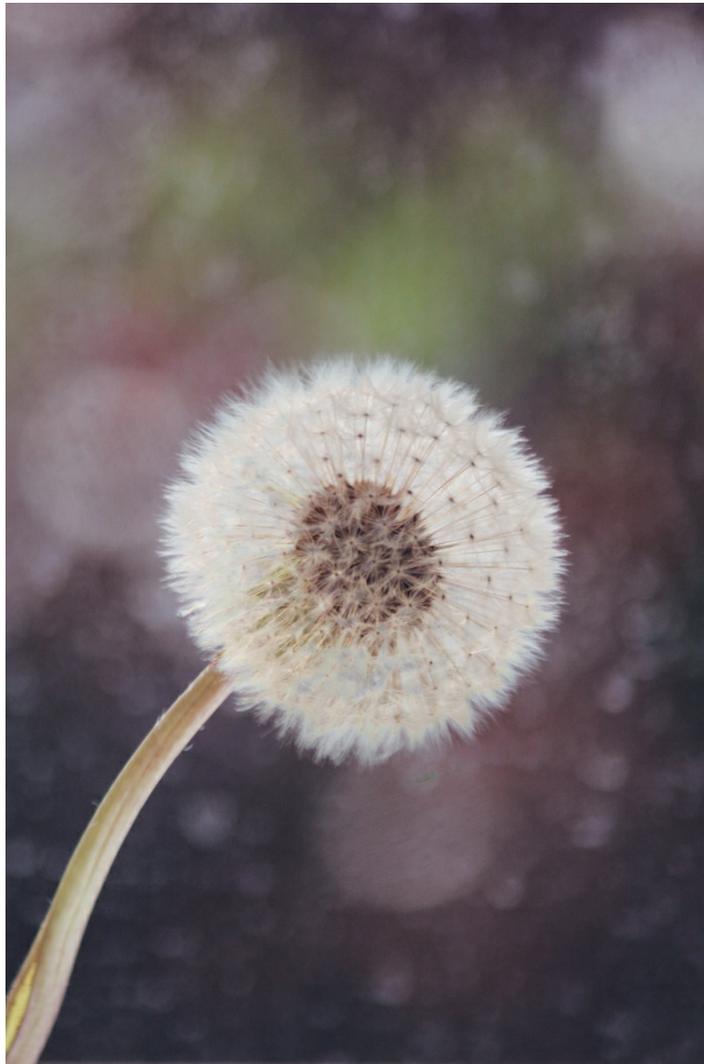
HD brain fluid makes brain cells grow clumps.

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It's like gardening gone wrong: scientists can sprinkle Huntington's protein on the outside of laboratory-grown brain cells and make sticky, potentially harmful protein clumps grow inside the cells. Now, new research showing that human brain fluid does the same thing could help us monitor Huntington's disease.

Huntington's disease is caused by a genetic mutation that makes the Huntington's protein extra-long. Just like an extra-long garden hose is more difficult to coil than a shorter variety, the extra-long Huntington's protein is more difficult to fold up than the normal version.

The added difficulty of folding the extra-long Huntington's protein causes problems for the brain, because misfolded proteins inside brain cells end up in sticky clumps that can make brain cells sick. Thus, brain cells that develop sticky protein clumps may be at risk in Huntington's disease.



The process of growing protein clumps from the outside of a brain cell in is called "seeding".

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A Few Bad Seeds

Scientists studying how these sticky clumps grow in the laboratory recently made an intriguing discovery.

For brain cells grown in a dish, sprinkling misfolded Huntington's proteins onto the *outside* of a brain cell made sticky protein clumps appear *inside* that same brain cell. Because of its parallels to the gardening you might do in your own backyard, the scientists called this process of growing sticky clumps "seeding".

There are two general ways that seeding could work in laboratory-grown brain cells. First, protein clumps could actually invade into brain cells from the outside, similar to the way that weeds from your neighbor's lawn might invade into your lawn. Alternatively, protein clumps outside the brain cells could cause the cells to change so that they grow new clumps inside on their own, similar to the way that changing your meticulous lawn-care routine to your neighbor's lazy one will make your lawn grow weeds (just like theirs). Either method - or even both at the same time - could contribute to how sticky protein clumps grow in the

laboratory.

While we know that seeding happens in the research laboratory, however, whether it happens in human Huntington's disease - or is instead just a neat laboratory trick - remains a mystery.

Another Use for Brain Juice

To answer this question, scientists at the University of California Irvine tested whether they could make seeding happen under more realistic conditions involving human "brain juice".

"Brain juice", also known as cerebrospinal fluid or CSF, is a clear liquid that surrounds the brain and protects it from injuries. CSF does a number of good things for the brain, like removing toxins and waste products.

This job of removing waste makes CSF a very good window into what's going on inside the brain. As an analogy, think of how much someone could learn about you by looking through your garbage - they could figure out what you eat, where you shop, and potentially even your credit card or bank information, just by looking at what you throw away. In the same way, looking closely at the CSF can help us to take a peek at what's going on in the brain.

"Human CSF can seed the growth of sticky clumps - and CSF from people with Huntington's disease does so much more readily than CSF from people without Huntington's."

One thing that CSF lets us peek at is the Huntington's protein. Even though we usually find the Huntington's protein inside brain cells, we know from [really cool work](#) that it also floats around in the CSF. This should make sense, because one of the CSF's most important jobs is removing toxins (like misfolded proteins) from the brain.

However, if misfolded Huntington's protein can cause seeding, then this clean-up job - in which CSF carries misfolded Huntington's protein around and then out of the brain - could actually put healthy brain cells in danger.

What Did They Find?

To find out if this is the case scientists, led by Steven Potkin at the University of California, Irvine, sprinkled human CSF onto brain cells growing in a dish to see if it could make sticky protein clumps grow inside the cells.

They tested three main varieties of CSF: CSF from people with symptomatic Huntington's disease (which has misfolded Huntington's protein in it), CSF from people without Huntington's disease (which doesn't have misfolded Huntington's protein in it), and CSF from people with the Huntington's mutation who aren't yet symptomatic (which is probably somewhere in between).

The scientists found that CSF from people with Huntington's disease seeded the growth of protein clumps much more readily than CSF from people without Huntington's. Further, brain fluid from people with **symptomatic** Huntington's was much better at seeding than brain fluid from people with **asymptomatic** Huntington's.

Thus, human brain fluid *can* cause seeding, and how readily seeding happens might be related to the severity of Huntington's symptoms.

What It Means

So, why should we care about all of these seeds and clumps - which are still just happening in a dish and not in people?



Even though this research is really interesting and well done, there are – as always – a few unresolved questions to keep in mind when considering the ultimate impact of this work for the Huntington's community.

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First, seeding might give us a new way to track Huntington's protein levels, and by extension disease progression, over time. Tracking disease progression is very important, because it lets us determine if Huntington's therapies being tested in clinical trials are effective. Historically, such tracking has required years of observation and been an inexact science, because clinical Huntington's disease varies so much between different people. Measuring disease progression via seeding might give us a more accurate or consistent - or at least faster - way to track changes happening in the disease.

However, there's still a lot of work to do before we can develop a disease-tracking method based on seeding. An important, early question scientists will need to answer is if things that make mice with Huntington's disease better actually affect whether mouse CSF can

seed the growth of protein clumps. If they do, we may be in business!

Second, these experiments could affect the search for new Huntington's drugs. We normally think about the Huntington's protein doing bad things *inside* brain cells. However, the seeding experiments highlight Huntington's protein in the CSF - which is *outside* brain cells. Therefore, this work serves as a reminder that Huntington's therapies might need to block the protein in both locations.

A Few More Questions

Even though the research we've been talking about is really interesting and well done, there are – as always – a few unresolved questions to keep in mind when considering the ultimate impact of this work for the Huntington's community.

First, we already knew that the Huntington's protein was in CSF, and we could already measure how much of it was there. So, why would we need to use seeding to track Huntington's disease in the first place? This is a tough question, because we won't be able to answer it until we test a seeding-based method for tracking Huntington's disease out for real. Nevertheless, it's quite possible that seeding, which looks at the Huntington's protein "in action", will give us more or different information than than we could get before. In general, having more information better equips us to follow the disease.

Second, even if seeding gives us a new way to track Huntington's disease, could a seeding-based method really be sensitive enough to detect how Huntington's changes over time or with treatment? The experiments we're talking about here weren't intended to answer this question, and so it's hard to tell if what the scientists saw in the laboratory will translate into a meaningful test in humans. The scientists are doubtless already hard at work figuring this out.

The Take-Home Message

Even though there are some important questions remaining – and a lot of future work to be done – these new results are interesting and relevant for the Huntington's community. They tell us about what the Huntington's protein might be doing and how it might be doing it, and they lay seeds (the good kind) for future research to improve the way we develop or track therapies. Like any good gardener, we just need to give these seeds the time they need to grow.

The authors have no conflicts of interest to declare. [For more information about our disclosure policy see our FAQ...](#)

GLOSSARY

CSF A clear fluid produced by the brain, which surrounds and supports the brain and spinal cord.

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