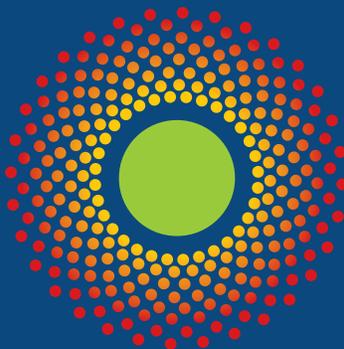


Enroll!

Updates from the Enroll-HD
global community



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AUTUMN 2015

DATA NOW AVAILABLE

Researchers worldwide can now access data from Enroll-HD

As of February this year, the first wave of data from Enroll-HD is now available for researchers around the world to ask new questions about HD. Making this first “data cut” available is a major milestone in the study. It is the culmination of years of effort by participants, site staff, study coordinators, quality control experts, information technology specialists, and many others who have joined forces to make it possible.

“It’s a huge and tremendous effort,” says Jean-Marc Burgunder, MD, chair of the European Huntington’s Disease Network executive committee. “To have this done in an organized way, and have this data cut, is tremendous.”

“It’s a huge and tremendous effort”

**- Jean-Marc Burgunder, chair of
the European Huntington’s Disease
Network executive committee**

The philosophy that motivates Enroll-HD is open access, so that any researcher at a recognized research institution, university or biomedical company can request the data through the Enroll-HD website. “The general thinking is that the more people who have a look at the data, the more information you can get out of the data, and the more use you can get,” says Burgunder, who is professor of neurology at University of Bern in Switzerland and affiliated with the University of Sichuan in Chengdu, China. Enroll-HD data is free to access, with very few strings attached: Researchers must sign an agreement stating that they will not try to identify any person in the study, and are asked to credit Enroll-HD in published work.

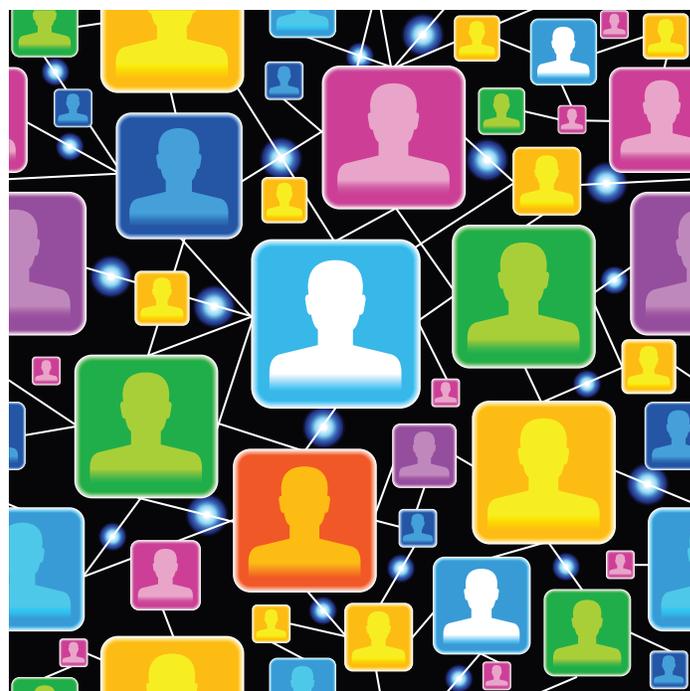
What does the data include?

Almost everything collected during an Enroll-HD site visit is made available, except any identifying information such as a name, date of birth or address. It includes basic information such as height, weight, and medical history—what

medications people have had, what nutritional supplements or other kinds of therapies they have had (e.g. sleep therapy), and also what other illnesses they have ever been diagnosed with. It also includes the results of all the tests that measure movement as well as how well people think, use words, remember things, and get through the day. Researchers can make special requests for other data that are not included in the dataset. (To protect privacy, this information is all stored with number codes separate from the ID in the study database. Real names are never used.)

How is the data readied for research use?

The data collected in Enroll-HD is released in big chunks rather than



continuously. That's because it has to go through a rigorous, labor-intensive quality control process before it can be used for research. A data monitor must make sure that forms are filled in correctly and that the small errors that often occur when filling out forms are caught and fixed. If a study physician writes down "ascian," did he or she actually mean to write "aspirin"? If one of the boxes is left blank, why?

The single most important part of quality control is to double-check that every person in the study has agreed to have their data collected and shared, and has signed the informed consent form that spells out this agreement. "That's really important to us, to make sure that anybody who participates in the study actually agreed to having their data collected and put into the dataset," says Eileen Neacy, chief operating officer at CHDI. A team of statisticians based out of Lisbon, Portugal also reviews the data to watch for combinations of answers that might potentially be used to re-identify a participant, and for hints that there might be a mistake.

"I think the database people have done an excellent job," says Douglas Langbehn, MD, PhD, a psychiatrist and biostatistician at the University of Iowa Carver College of Medicine who is one of the early users of the data.

Above all, the main focus before a dataset is made public is to make sure that the information can't accidentally identify somebody who has a distinctive characteristic. For example, if someone has an unusually long CAG repeat—say, 62—it could in theory be possible to figure out who that person is since the number is not common. So that CAG number will be "aggregated" in the dataset; rather than include the specific number, it will be recorded as "more than 55." Or if one participant in the database has a fairly unusual condition such as a left foot amputation, it's possible that someone who knew them and also requested data access could put two and two together. It's highly unlikely but since it's theoretically possible, the team will either aggregate that information (list it as "limb amputation," for example, rather than naming the specific kind) or withhold that record from public access until the study becomes large enough that it includes other people who also happen to be missing a left foot.

Ultimately, a major point of Enroll-HD is to provide broad access to the maximum amount of data, because it leads to stronger, better science. "We want to get as much of the data as possible to researchers, because they are more likely to find statistically significant and interesting findings," says Neacy. But the first commitment is always to the people who have volunteered to be part of the study.

PUTTING DATA TO WORK

One example of how the observational data from Enroll-HD is already being put to work is in the research of psychiatrist and biostatistician Douglas Langbehn, MD, PhD. He hopes to get a more precise sense of exactly how the disease unfolds, an extremely important step in treating or preventing the disease. "In order to be able to eventually tell if a treatment for HD is effective, we have to understand as much as we can about the natural trajectory of HD in the absence of treatment," he says. "How quickly do things change? What sorts of things change together?" Knowing that will make it much easier to see whether a proposed therapy is working and avoid long, expensive trials of drugs or therapies that turn out in the end not to do any good. "We wouldn't expect a treatment for HD to cure somebody overnight," he says. What's more likely is that a treatment will slow or stop the changes caused by HD over time. Langbehn adds: "How do you know what that is, if you don't know the changes over time in the first place?"



Langbehn has worked in the past with data from other big observational studies like PREDICT-HD, TRACK-HD and COHORT in the US, and he will analyze the Enroll-HD data to understand more about the rate of progression—why different symptoms emerge at different times for different people and whether this can be predicted. "The hope is to eventually be able to test preventive therapies for HD that we can give to people before they are clinically ill," he says.

What will people use the data for?

Researchers will be able to explore a huge range of subjects with this data, but one obvious goal is to better understand what predicts the advance of HD, suggests Burgunder: "You need to have a large number of patients followed up for a while to make a prediction." Because it includes so many people, Enroll-HD data could help explain why some people experience emotional symptoms from the disease, while others are more affected by

cognitive or physical manifestations. Understanding why these patterns are different from person to person, or understanding why some people get symptoms later than others who have the same number of CAG repeats, could be a big step forward toward finding effective treatments for HD.

And since Enroll-HD includes people from many of the world's major geographic regions, the database also makes it possible to explore cultural and environmental influences on HD. Burgunder, for example, is working on a project to compare how HD presents in Europe and in China to identify potential differences. Psychiatric symptoms, for example, might be quite different in China as compared to Europe or the Americas, or they may be much the same. Either way, that's important to learn and then to figure out what might cause those differences. "That's important for treatment strategies and guidelines," he says: Making sure that people get the treatments they most need. "Enroll-HD will be tremendously helpful in this."

Other projects that are making use of Enroll-HD data include research to predict how quickly individual people's symptoms will progress, an exploration of changes in physical symptoms over time to identify how best to measure potential benefits from physiotherapy, and several projects to measure the validity of one version of the "Problem Behaviors Assessment," the test that is currently used to gauge problems like depression, irritability or apathy.

How it works

The first dataset only includes information gathered before January 1, 2015, because it takes time to review and correct all the records prior to release: 1457 people in all. That is just the first chunk. Ultimately, the Enroll-HD database will include at least 10 times as many people, and include far more data on each participant as people complete followup study visits year after year. The organizers plan to release the next dataset before the end of the year. Eventually, releases will be planned roughly once a year.

To request access, researchers apply for an account through the Enroll-HD website. They must be affiliated with a known institute, company, government or nonprofit research organization. They must agree in writing that they will not try to identify any participants. In return, they are granted access to a restricted area of the website where they can download the data themselves. Researchers seeking access to the data are asked to provide a short description of the research project they are planning, which is posted publicly on the website to encourage collaboration with other researchers who have similar interests, and to inform participants.

If researchers publish based on Enroll-HD data, they are asked to acknowledge the participants and the researchers of the study.

It is an unusual arrangement. In medical research, most databases are either proprietary (owned by a company) or available only to the team that collects the data. "One huge element of Enroll-HD is the idea of open access to the database," says Langbehn. "It will encourage people to be able to pragmatically test out hypotheses that they may have about how the different clinical elements of HD go together."

With REGISTRY, the European observational study that preceded Enroll-HD, the idea of open data sharing was still fairly new, so researchers were required to apply for data access. Now, more than ten years later, the guidelines and procedures for ensuring privacy protection are better established, so the process can be simpler and faster, says Burgunder. Making access simpler and faster will increase the number of researchers who would be interested in working with the data, even researchers who don't usually work on HD. "It will encourage more people to become involved in HD research," says Langbehn, who works with CHDI to review and improve some of the documentation that goes along with the datasets. In his own research (see sidebar, "Putting Data to Work"), he focuses on understanding the natural trajectory of HD over time in order to develop methods to accurately assess future therapies designed to slow the progression of the disease.

Researchers can also apply to work with biological samples collected as part of Enroll-HD, including DNA. (This is an optional part of the study: Many participants agree to have blood samples collected for use in research.) Here too, the idea is to make the samples available as a public resource for the broader scientific community, but there are a few more rules. Since the samples are expensive to collect and store, to offset these costs and ensure that researchers will make good use of the samples they are asked to pay a processing fee. And because some samples aren't renewable, researchers must describe the scientific rationale for any project that seeks to use these particular samples; such projects will be reviewed and approved by an independent scientific committee.

Getting Enroll-HD data ready for research was a massive joint effort, says Burgunder, the work of many people collaborating to solve a vast number of logistical questions around the world. And this is just the beginning. "This is tremendous," he says. "And the next datasets will be larger and larger as we go ahead."



SLEEPING ON IT

New research may help people with HD rest easier

As anybody from an HD family knows, getting enough sleep can be a challenge. In one survey in the UK, 88% of people with HD said they had sleep problems, including waking up in the middle of the night, restless leg movements in bed, waking up too early in the morning, or being sleepy all day.

It's more than just ordinary insomnia. Emerging evidence suggests that HD somehow disrupts the circadian clock, the internal mechanisms in the body that keep us in synch with the 24-hour day. So it's not just sleep that gets off-kilter; it's also cycles in appetite, body temperature, and hormones. The result is that people with the HD gene expansion may feel perpetually out of synch. It's as if they were jet-lagged all the time, says researcher Chris Colwell, PhD, an expert in sleep and circadian rhythms at the University of California, Los Angeles.



"There are a number of things that go wrong when you disrupt these clocks—things that everyone has experienced when acutely jetlagged. Memory is difficult, you feel fatigued, you have difficulty focusing," he says. "There are effects on cognition, and even some things like mood." It can make people irritable and confused, more sensitive to stress, and it can throw metabolism out of whack. Feeling this way all the time can take a toll, especially since people with HD may already be struggling with some of these problems.

Despite how common sleep difficulties are, they haven't been a major focus of HD research. That is beginning to change. Several researchers have recently explored why people with HD often have trouble sleeping, and also investigated mouse models of the disease to understand more about the biology of the circadian clock problem. Even though the

cause hasn't yet been pinned down, some simple behavioral changes might help reset the clock in people—a possibility researchers are now studying. "We believe we can improve the quality of life for the person," says Colwell. "If you're sleeping better, it wouldn't surprise me that you were doing everything better."

What goes wrong

It's now well established that the cycle of sleep and wakefulness in people with HD is disrupted. The hormone melatonin, which is controlled by the body's internal clock and helps people sleep, is supposed to increase at night and decrease in the morning. In people with the HD gene, it may begin increasing at any time of day, out of phase with the 24-hour clock. For some people, this happens well before official diagnosis.

Similar problems develop in mice that have been genetically modified to carry the HD gene and develop symptoms. The animals, normally nocturnal, become more active during the day. (They are monitored via video analysis, or by remote sensors that detect heart rate and body temperature.) Genes that regulate the circadian clock are disrupted, and the animals show other signs of being out of synch.

These observations led University of Cambridge neurobiologist and HD expert Jenny Morton to propose in 2005 that sleep problems and circadian disruption may be a core part of the disease, not simply a knock-on effect of other symptoms. A later study showed that in HD mice, drugs that restored more normal sleep patterns helped the animals learn and think better.

So the search was on for ways to resynchronize the system in humans—ideally through changes in behaviors rather than drugs, since they don't have side effects and are often more effective than drugs over the long term. The most obvious regulators of the sleep-wake cycle are food, exposure to light, and exercise, says Colwell. Some practices, such as keeping the bedroom cool and dark, limiting alcohol and caffeine, and avoiding computers and other bright electronic devices before bed, are recommended for anyone who is having sleep trouble, whether they have HD or not. Morton distilled much of this advice in a 2013 paper and summarized it for a story on the research news website HD Buzz, "Simple rules for a good night's sleep."

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PEOPLE
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FOR ENROLL-HD
IN 12 NATIONS
AS OF SEPTEMBER 16, 2015

Both Morton and Colwell have also looked to mouse studies for more answers. In 2013, Morton's group found that HD mice allowed to eat only at night (when they are naturally awake and active) kept their weight on for longer, and had better motor performance. The group also found that treating mice with bright light right before nightfall and allowing the animals to exercise only at night helped restore more normal circadian patterns. Colwell has found that limiting feeding times makes the biggest difference. In a study that has not yet been published, he also found that allowing HD mice to eat only at night delayed the onset of their motor symptoms.

"The timing of when you eat can help or hinder the synchronization to the environment," he says. "The liver and the gastrointestinal system lock on to when the food is available, and even parts of our brain." Eating on a regular schedule is a trick to put the metabolism on a 24-hour cycle, and that can translate into a more regular pattern of sleep and wakefulness.

Could it help us?

This summer, Colwell's group began recruiting people who have been diagnosed with HD to measure how well they sleep. They will wear a wrist band like a Fitbit to monitor sleeping, movement during sleep, heart rate and heart rhythm.

In the meantime, although these interventions haven't yet been shown to work in humans, there isn't much risk

or major downside to trying it out, suggests Colwell. "You don't have to have something injected into you. These are commonsense, and might help anyone out," he says, even someone who doesn't have the HD gene but is having trouble sleeping.

"If you're sleeping better, it wouldn't surprise me that you were doing everything better."
-Chris Colwell, UCLA

For a human, the equivalent practice would mean eating most of your calories on a regular schedule during a six to eight-hour window during the day, well before

bedtime. That doesn't mean eating less or more food; it would be the same amount, but keeping to the schedule. Exercising during the first half of the day (or at least three hours before bedtime) also has been shown to help human insomniacs who don't have HD, and Colwell thinks it may also help people with the disease.

Based on his results in HD mice, Colwell thinks that circadian problems actually accelerate the advance of HD. He hopes that helping people resynch might actually delay the onset of some of the other manifestations of the disease. In any case, improving sleep and getting more in tune with the daily clock could make life easier and healthier, both for people with HD and those who love them, says Colwell: "At the very least, we can improve the quality of life for patients and family members."



HUNTINGTIN-LOWERING TRIAL BEGINS

The first test of a treatment intended to lower the amount of the protein that causes HD was administered to its first patient on September 3rd, 2015, according to the study sponsor Isis Pharmaceuticals. The treatment, ISIS-HTT-Rx, is a short stretch of DNA that is designed to reduce the production of the huntingtin (HTT) protein by blocking the process in the cell that "reads" the gene. ISIS-HTT-Rx is delivered via lumbar puncture (an injection into the base of the spine, near the spinal cord) and will be given at four different concentrations to see which dose works best (if at all).

This study will enroll 36 people with early-stage HD at sites in Canada, the United Kingdom and Germany. The major focus is to see whether the treatment is safe and doesn't cause side effects, but researchers are also looking for beneficial effects, such as a lowering of the mutant HTT in treated patients. If there are no major problems, the next step would be to test whether it actually slows the progression of HD.

This will be the first time that a huntingtin-lowering therapy will be tested in people, but it's not the first time this type of treatment has been used: Isis Pharmaceuticals already has succeeded with one gene-blocking drug, Kynamro, which effectively treats a rare inherited genetic disorder that causes extremely high cholesterol.

FIND OUT ABOUT STUDIES

To help people who are interested in joining clinical trials for HD treatments but don't know where to look, the Huntington's Disease Society of America has launched an online HD Trial Finder at www.hdtrialfinder.org. It's a

centralized place to easily find out about all institutionally-approved studies of HD in North America.

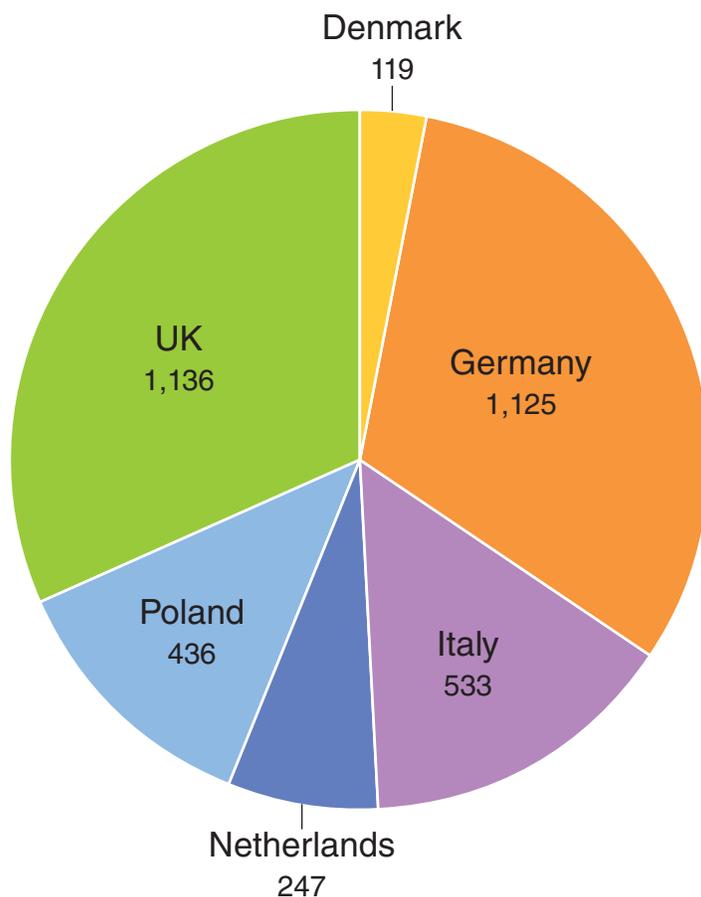
To use it, you can browse through all studies that are ongoing (including drugs, other therapies for HD, and

other types of studies), or you can fill out a profile including your HD status and some basic medical information that will be automatically matched against studies that are recruiting new participants. The service is free to use.

GROWING FAST

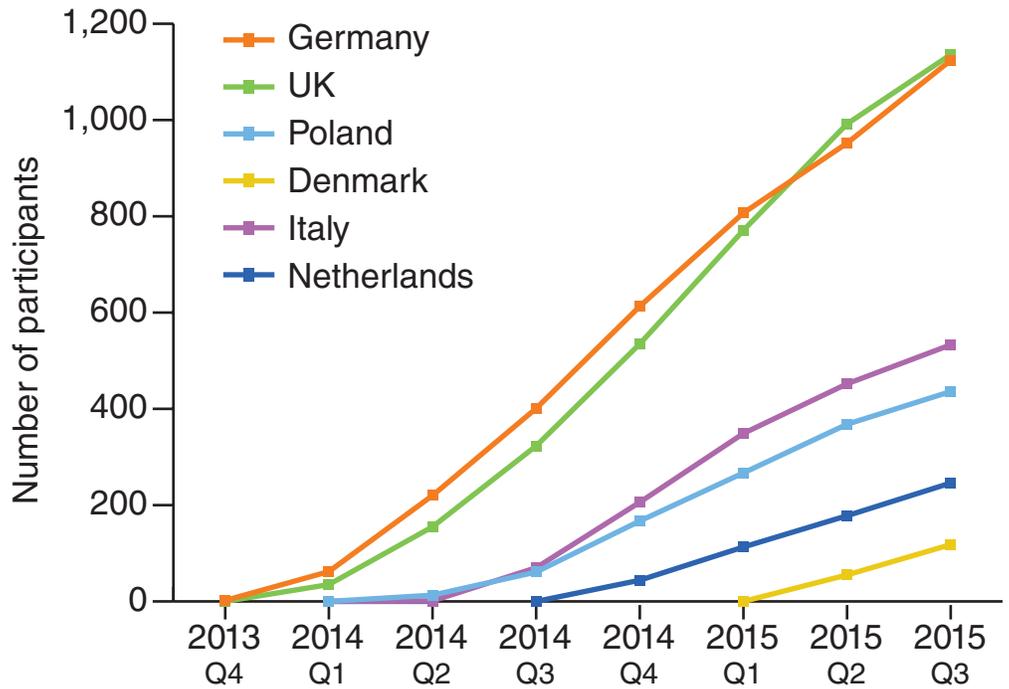
Change in Europe: The transition from REGISTRY to Enroll-HD is moving quickly in Europe. REGISTRY included 17 nations and more than 12,000 participants, and safely transferring all that information to the new system is a big job.

More than a third of the 132 sites in Europe are now part of Enroll-HD. In Poland and Denmark, the transition is complete; Germany, the UK, Italy and the Netherlands are nearly there. France, Spain and Ireland will be next. (Numbers updated on 16 September 2015.)



European participants in Enroll-HD by nation; the study launched first in Germany and the UK.

Quick Start: The chart tracks how many people have joined Enroll-HD in the six European nations where the study is now up and running (as of September 2015). Because most of those study sites had been part of REGISTRY, the European study that came before Enroll-HD, enrollment has grown rapidly once the transition from one study to the other is finalized. Enroll-HD is “activated” country by country; a site in Germany was the first to make the transition in November 2013, followed by other sites in that nation and in the UK.



In the nations where Enroll-HD has launched, numbers are growing quickly.

Q&A

RESEARCH UPDATE

*What's a Huntingtonologist?
Q&A with Hugh Rickards*

People with HD may consult with a psychiatrist, a neurologist and a psychologist for their diverse symptoms, but what they really need, says Hugh Rickards, FRCPsych, MD, is a “Huntingtonologist”: A doctor who has been trained in all the diverse manifestations of the disease, from motor control to emotional issues to cognitive changes. Rickards, who is consultant in neuropsychiatry and honorary professor at the University of Birmingham, says that the emotional and cognitive problems of HD tend to get underplayed by doctors and researchers—



Hugh Rickards

and it shouldn't be that way. Rickards is a neuropsychiatrist at a large clinic for people with HD, and is also involved in recruiting people for research, including Enroll-HD. His own interest in the emotional landscape of HD has led him to spot similarities between HD and Asperger's syndrome, the autism-like developmental disorder involving difficulty understanding other people's feelings and states of mind.

What got you interested in HD?

I'm always interested in things that are between mind and brain, and it's difficult here to see where physical stops and mental starts: Mood, physical condition and cognition all mixed up together.

Why do you talk about HD as “acquired Asperger's syndrome”?

I think there is increasing evidence that people with HD in mid age start to acquire the social and cognitive deficits of Asperger's: The insistence on sameness, lack of empathy,

difficulty in tests of “theory of mind,” and inability to understand people’s states of mind.

The main ones are the inability to understand other people’s states of mind, and inability to do future envisioning, that is to say: envisioning alternative scenarios apart from the one that is there at the moment. Both are all about the inability to imagine something that’s not happening right in front of me right now. That requires a sort of mind’s eye, and people with HD seem to lose that.

It’s hard on people around them. In clinic, you might ask the patient how they’re doing and the patient says they’re fine. But the wife or husband sees the trouble. The patient doesn’t understand what’s happening—or the partner’s distress. These are fundamental deficits in HD, and they’re the most disabling.

It’s an interesting idea, but why does that matter for people in HD families?

It makes a massive difference. If you understand the mental state of HD, you can help carers manage better, which could mean the difference between them staying at home or being in a nursing home. For example, if you ensure that their environment is quite predictable, you might do quite well, whereas if you keep treating them as the same old person they used to be, you might end up in a lot of fights.

Why do you say that we should train doctors as “Huntingtonologists”?

If I ruled the world, we’d train people in the whole of HD: the complex mental changes, the complex motor and cognitive problems we see. I don’t think you can understand those things in isolation.

There’s no such thing as “just movement”; it involves cognition, mood, and mental state. To separate them is a philosophical error. Anyone who knows anything about how humans work knows that motor and cognitive and emotion systems are intrinsically part of one another.

I think that research needs to think of more subtle ways of understanding the relationships between *motion* and *emotion*. My personal view is that we [in HD] are hung up on motor disorders. We’ve privileged that as being the big deal, and I don’t think it is. Emotional symptoms are quite often early and quite often devastating.

Motor disorder *is* a cognitive disorder, by the way: Isn’t a motor disorder coordination? And isn’t that cognitive? It’s semantic, really. But it stops us from developing more meaningful language.

What kind of research are you doing now?

I’m primarily a clinician with an interest in research. I’m interested in [neuro]imaging of social cognition, and the biology of social cognition. There’s a story that would suggest that social cognitive deficits might be mediated by oxytocin [a brain chemical involved in relationships].

You have a big clinic, with about 350 patients with HD, and you’ve been working with HD for more than 20 years. What keeps you going?

The patients are great. They have a horrible illness, but they really like to do research. Also, the global research effort has been fantastic. We’ve got a good collaborative approach.

The biggest thing for me, is that when I started as a junior doctor, everybody with HD was in the back wards of the asylums and thought of as being not treatable. Now, they’re giving the first gene suppression to people with HD [see “Huntingtin-lowering trial begins”, p. 5]. What could be more exciting than that?

Enroll! is a publication of CHDI Foundation, Inc., a not-for-profit biomedical research organization that is exclusively dedicated to rapidly developing therapies that slow the progression of Huntington’s disease (HD). As part of that mission, CHDI Foundation sponsors and manages Enroll-HD. More information can be found at: www.chdifoundation.org

Editor: Simon Noble, PhD

Senior Science Writer: Kat McGowan

Layout: Katherine Vicari

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