HUNTINGTON'S DISEASE NEWSLETTER 2025

John Van Geest Centre for Brain Repair & Addenbrookes Hospital

Welcome to our latest newsletter!

First of all, thank you all for your continued support with our research and thank you also to the team for all the hard work they have put in over the last 12 months to try and improve our understanding and treatment of HD. We are also very grateful for the continued support and help from our specialist HD advisors, Dawn and Rachel, who provide us with the valuable link between our clinic and the community. This is so important especially as the clinic is as busy as ever and it is great to have Tom fully involved and helping deal with the ever-increasing demand on our service. In this respect, we are very lucky to have Josephine take over from Lindsey in helping co-ordinate this clinic as well as Katie, Amy and Miriam who continue to undertake assessments and studies linked to the clinic such as ENROLL-HD. More recently we are fortunate to have Sarah (Mason) come back to join us, albeit part time, after finishing her training in clinical psychology- she is not only now developing some of her own research but is offering some therapy to patients in need of psychological support.

On the research side we have had a very successful year. We have been heavily involved in exciting new trials with companies looking to stop the production of abnormal mutant huntingtin with the hope that this will slow down disease onset/progression. Linked to this we have now finished our own trial, FELL-HD, that sought to increase the clearance of this protein (rather than reduce its production) using a drug that is used in the clinic already to lower blood pressure, felodipine. This drug has been shown to help cells and animals with HD in the lab so it was logical to see whether it would work in the clinic as well. Although our trial was not powered to show whether it slowed down HD, it did show the drug was well tolerated. The question is now what we do next in this therapeutic area and we are currently deciding on this.

Another exciting area of research has been in sleep, where Zanna and Mehak have shown that problems in this occur early in HD and are associated with changes in thinking as well as evidence of cell loss/damage in the brain. Of course, this raises the question as to whether the cells affected by mutant huntingtin cause problems in sleep and thinking independently of each other, or whether the problems in sleep then make the pathology and problems of HD much worse. To answer this we need to do a trial to target sleep and see what effect it has in early HD and we have now just received funding to start such a study from LifeArc. All very exciting.

To facilitate all these trials it would be good to have better markers of disease onset and progression and although some have emerged in our work on sleep, we are also exploring this using blood samples and more recently by studying the eyes in great detail. Although early days, some of these tests are looking promising.

Finally, we have started some new work looking at what may be driving some of the problems in the brain in HD around so called jumping genes or transposable elements (TEs). These TEs make up about half of our DNA and their function is unknown. We are now looking to see whether they get switched on in the brain in HD and whether this then drives the disease process and if so, whether we can we do anything to stop this. This work involves looking at human HD brain tissue kindly donated by patients who have passed away as well as in cells grown in the lab using special techniques.

So, all in all, an exciting year and lots to think about and work on- none of which would have been possible without your generous support and encouragement. Thank you.

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Meet the team!

Roger Barker
Professor of Clinical Neuroscience and Consultant Neurologist

Tom Stoker
Consultant Neurologist

Katie Andresen
Clinical Research Manager

Amy Evans
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Zanna Voysey
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Sarah Mason
Clinical Psychologist

Josephine Mordi
Clinic Coordinator

Miriam Schaepers
Research Assistant

Sophie Field
PhD student

Angelica Guiloff
PhD student

Mehak Malhotra
MPhil student

Will Woods
Clinical Fellow

Shaline Fazal
Laboratory Research Manager

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Huntington's Disease NHS Clinic

Clinic Contact Details

To reach us please leave a message on the HD clinic answer phone or email the clinic and we will get back to you. We aim to respond to queries within 3-5 working days.

HD clinic direct line: 01223 761863

HD clinic email: add-tr.hdclinic@nhs.net

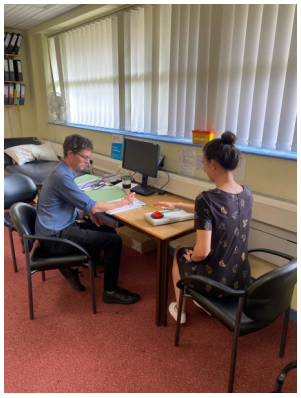
Our clinics are running well with Monday continuing to be phone and video calls; these are done using zoom so please ignore any Teams links from the hospital that get sent. **Any links to be used will be sent directly from our clinic email.** Wednesdays are face to face appointments. Our appointments are increasing in numbers, both virtual and face to face, with an increase of 11.8% last year as well as 41 new patients joining our clinic.

Many of you will have met Dr Tom Stoker now and know our clinics are run by Roger and Tom on Wednesdays to enable us to offer a full day clinic. As always we thank you for your patience and flexibility with us when it comes to booking your appointments and dealing with queries you may have

At the beginning of the year, we said goodbye to our long term clinic coordinator Lindsey Robinson who moved onto new endeavours. Josephine Mordi has since joined our team and will be your main point of contact for queries and appointments.

Appointments

Our clinics do constantly remain fully booked. If you can not attend or need to rearrange please let us know as soon as possible as we currently have over a 4 month wait.



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Huntington's Disease Association

Dawn Stilwell: Specialist HD Advisor (HDA)
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Email: dawn.stilwell@hda.org.uk

Rachel Boothman: Specialist HD Advisor (HDA)
Telephone: 01536 211496
Email: rachel.boothman@hda.org.uk

Dawn is the Specialist Huntington's Advisor for Cambridgeshire, Norfolk, Suffolk, and Essex, while Rachel covers Hertfordshire, Bedfordshire, and Buckinghamshire. Both enjoy supporting individuals and families living with Huntington's disease (HD) and work closely with local HD clinics to coordinate care and community support. They offer home visits, phone or video consultations, and attend support groups. They also provide information on local branches and peer support opportunities. Regular events covering various aspects of HD are held throughout the year. The Huntington's Disease Association (HDA) runs both in-person and online support groups, as well as webinars and other events. For updates and future events, visit the HDA website at www.hda.org.uk. You can also sign up for email updates via the 'keep in touch' link: www.hda.org.uk/get-involved/communication-consent or follow them on social media.

Psychological support in HD

After a three-year break to complete my clinical training, I returned to the HD clinic this March having qualified as a clinical psychologist. I currently work 1 day a week, although hope to expand this in the future. Whilst here, I will be focused on developing our long-term aim of bringing better psychological support to people with HD and their families. Clinically, this will include helping people to access appropriate support in the community where available and providing a small number of clinical sessions to support people who are not able to access support locally to them. I will also be working closely with commissioning bodies to understand the barriers which prevent people with HD from getting the psychological support they need.

A big part of this work will include developing up a program of research to better understand how changes in someone's ability to recognise, understand and respond to the thoughts, feelings and emotions in other people (also known as their "social cognition") relate to *"behaviours that challenge"* in HD. Behaviours that challenge are behaviours that may pose a risk to the person with HD or other people, or that significantly impact on their quality of life or access to care. We intend to focus on behaviours such as apathy, irritability and financial or social vulnerability where we believe that getting a better appreciation of what underpins these changes will improve our ability to respond to and manage these difficult aspects of the disease in the clinic.

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FELL-HD study

Funded by UK Dementia Research Institute

In September 2022, we launched the Fell-HD trial, a study inspired by groundbreaking work conducted in Cambridge by Professor David Rubinsztein and his lab. They studied ways to clear away the abnormal mutant huntingtin seen in Huntington's Disease (HD).

The main intervention in the Fell-HD trial was the administration of felodipine, an oral medication already licensed for use in humans to lower blood pressure. Preclinical experiments in David's lab had demonstrated promising results, showing that felodipine could reduce aggregates of the huntingtin protein in cells. One key advantage of repurposing an existing drug is knowing its safety profile and the side effects. However, because we were using felodipine differently— namely in people without blood pressure problems, it was essential to test whether it was both safe and tolerated in people with HD. Additionally, we aimed to explore any early indications that it might slow disease progression.

To better understand this aspect of felodipine, we conducted a sub-study, Fell-HD-s. This study focused on disease markers known to track HD progression, allowing us to assess how felodipine might influence them. Every participant in the main Fell-HD trial kindly agreed to take part in Fell-HD-s. Together, the studies included a range of assessments, such as brain MRIs, spinal fluid and blood collection, and clinical tests. By combining these measurements, we aimed to uncover whether there was any signal suggesting that felodipine could slow the progression of HD.

The Fell-HD trial completed recruitment in February 2023 and officially concluded in spring 2024. We are now in the process of synthesising and analysing the results, a critical phase that will determine what insights this trial can provide for people living with HD. What we so far can say is that the drug was well tolerated in HD. If you would like to know more about this trial, please contact Katie via email kera2@cam.ac.uk or telephone 01223 331141.

Participants underwent MRIs as part of the trial

FELL-HD

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Silencing the abnormal Huntington's gene

Funded by Roche Pharmaceuticals

We have been involved in trials to investigate the impact of silencing the abnormal HD gene product (mutant huntingtin) since 2016 which were originally funded by IONIS and then by Roche pharmaceuticals. The agent, called an antisense oligonucleotide or ASO, has been designed to lower the level of the protein huntingtin in the brain by telling cells to delete the 'message molecule' that is being coded for by the huntingtin gene. The American Pharmaceutical company IONIS began the trials back in 2016 with the initial results published in 2019. Roche then bought the license to the drug in 2018 and renamed the agent Tominersen.

Since 2019, we have been involved in all of the Tominersen trials. Gen Extend was an open label treatment trial meaning all participants received active drug and this aimed to provide answers about the long term safety and tolerability of Tominersen. Generation HD1 was a double blind, placebo controlled trial, meaning the participants and trial team did not know who was receiving active drug or placebo (a pretend drug) and aimed to determine whether Tominersen actually does slow down the progression of HD in a clinically meaningful way.

In March 2021, Roche announced that dosing would be permanently halted in the Generation HD1 and Gen Extend trial. This decision was not based on any new emergent safety concern, but on a broad risk/benefit assessment of treatment arms compared to the placebo arm over time in the Generation HD1 data.

After a post-hoc analysis of the Generation HD1 trial, this suggested that Tominersen *may* have a potential benefit in a subgroup of patients. In 2024 Roche activated the Generation HD2 trial. This new double blind, placebo controlled trial recruited a younger adult population with prodromal and early manifest Huntington's disease. This trial aimed to recruit 300 participants across 4 continents to receive either 60mg or 100mg of Tominersen or a placebo every 4 months.

In April 2025, Roche announced that after an independent data monitoring committee review, it was recommended that the 60mg dose should be discontinued and the trial continue only with 100mg dose, which was judged to more likely have a clinical benefit. This doesn't imply that the 60mg dose is ineffective or that the 100mg dose is definitively effective—it simply indicates that, based on current observations, the higher dose appears to be the more promising option to pursue further .

The trial closed to recruitment in December 2024 and all participants are now in follow up, we are an active site in this and recruited 3 participants to this trial. This trial is being run by Katie and Zanna at our site.

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Lowering the mutant huntingtin levels

Funded by Alnylam Pharmaceuticals Inc

Alnylam Pharmaceuticals have designed a trial to investigate a new drug called ALN-HTT02 in people with Huntington's disease. ALN-HTT02 is injected into the spinal fluid of the participants via a lumbar puncture to ensure it gets to the brain.

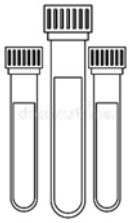
This is a first in human trial, so the main aim is to test the safety and tolerability of the drug.

ALN-HTT02 works by interfering with the messages from the faulty gene that causes HD and hopes to reduce the amount of mutant huntingtin (the cause of HD) being produced (similar to the tominersen drug, see page 7).

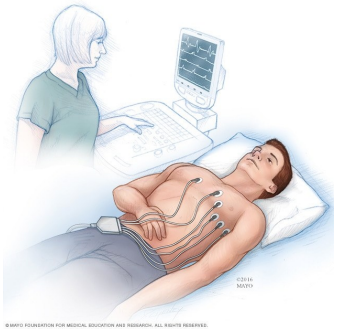
The trial is designed as a randomised, double blind, placebo controlled trial meaning that neither the participants, nor the study team know what a participant is receiving, active ALN-HTT02 drug or placebo (a pretend drug). It is completely random who receives active drug and placebo. The main difference between this one and the tominersen trial is that ALN-HTT02 is administered only once, whereas tominersen is administered every 4 months.

The trial is expected to last for at least 14 months, with the option to extend by a further 12 months per participant meaning the trial itself is expected to run for around 24 months. Overall, the aim is to enroll 36 to 102 participants who have been clinically diagnosed with early signs of HD across all sites. The trial involves clinical assessments, blood samples, spinal fluid samples and MRI scans.

Katie and Zanna are going to be running this trial at our site in Cambridge and are recruiting this year. If you are interested in participating or would like to hear more, please contact Katie on kera2@cam.ac.uk or 01223 331141.



Participants have blood panels done as part of the safety measures



Participants have regular clinical visits involving assessments such as ECGs which record activity of the heart and vital signs taken to measure things like blood pressure, temperature and heart rate

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ENROLL-HD

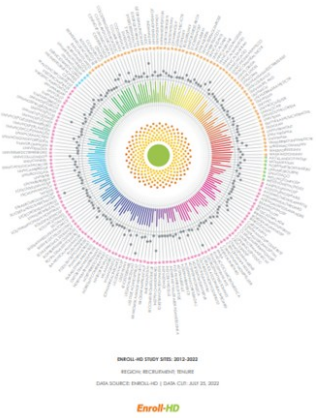
Funded by Cure Huntington's Disease Initiative

The Enroll-HD study is the world's largest observational study with around 21,500 participants from over 155 hospitals and 23 countries. In Cambridge, we have 115 participants who take part. During 2024 we completed 75 follow up visits and re-cruited 5 new participants.

Study visits involve completing questionnaires, memory tests and giving a blood sample along with the normal as-sessments that are usually completed in clinic. An anony-mised version of the data from Enroll-HD is available to all researchers from any site involved in this work. This means that we have access to information on a very large number of people with HD, from all around the world, that can help us understand more about this condition in a fast and efficient way that was not possible before.

An amendment to the Enroll-HD protocol is under development. The new study protocol, called Enroll-HD 2.0, will include different assessment batteries based on disease progression, a wider variety of bi-osamples, and sub studies (such as imaging and saliva collection). The amended protocol will focus on recruiting younger people and people with no, or very few, clinical features.

Within Enroll-HD there are sub-studies which are optional extras to the main Enroll-HD study. The plasma collection study is an annual blood test across 5 years. We currently have 41 participants in this study, and some of our partici-pants are reaching their year 3 sample. We have also started a sub-study called the **Later Stage Assessments study**, this opened in Autumn 2024. The study seeks to develop a series of assessments that are more appropri-ate for patients with advanced HD. If you are eligible, you may be asked to participate in either or both sub-studies when you come to your Enroll appoint-ment.



If you are already enrolled and would like to contact us about your follow up appointment, or would like to participate, please contact Amy on ahe28@cam.ac.uk or 01223 747489.

HD Clarity

We are involved in the HD Clarity study, which is a multi-site cerebrospinal fluid (CSF) collection study in HD patients. CSF is an ideal fluid compartment for assessing HD biomarkers due to its proximity to the brain. It is collected via a lumbar puncture and can facilitate the identification and development of new biomarkers, as well as exploration for potential targets for intervention. This study works in collaboration with Enroll-HD and we currently have 15 active participants. We are still actively recruiting to HD Clarity.

If you would like to hear more about this study or would like to participate, please contact Katie on kera2@cam.ac.uk or 01223 331141.

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Sleep in HD

ASSOCIATION OF BRITISH NEUROLOGISTS

Funded by Association of British Neurologists

Zanna is continuing her work on sleep problems in HD, aiming to better understand and find out whether treating them might help HD symptoms or this aspect of Huntington's.

This is an area growing in momentum, as Zanna has now been joined by MPhil student Mehak, and has recently elected to stay on in the group after her PhD to work on this area for at least another three years.

We have had some really exciting results from our observational study in this area, and Zanna has been busy getting them published and presenting them at lots of conferences.

Firstly, we found that subtle changes in sleep begin and evolve decades before HD becomes symptomatic, and this could in the future help predict when someone is likely to start showing the first features of HD.

Secondly, we found that HD gene carriers who have lots of insomnia during the night tend to have more problems with thinking – especially with memory, attention, information processing and planning - and higher levels of a blood protein that suggests their HD is more 'active'. This suggests that the insomnia may be 'aggravating' HD, and that by treating it, we might be able to improve things.

Until recently, good treatments for sleep in HD have been hard to come by, but excitingly, this is now changing thanks to the emergence of several new therapies. We've been working hard to try to secure funding for a trial of one of these therapies which will hopefully start soon, so watch this space!

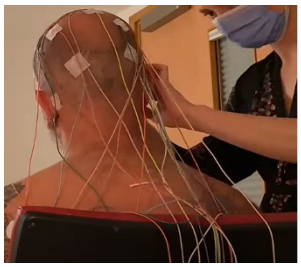
A huge thank you to all the participants who made this study possible!

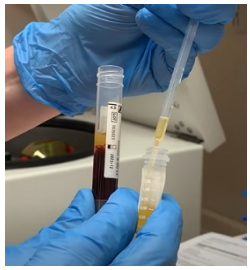
Here is a link to an HDBuzz Twitter piece about the work:

https://tinyurl.com/228ytwmy

And here is a YouTube video we recently made about the study:

https://tinyurl.com/4mpdwnvu





Snapshots from our recent NIHR video showing electrodes used to record sleep brainwaves and blood samples to measure the sleep hormone melatonin

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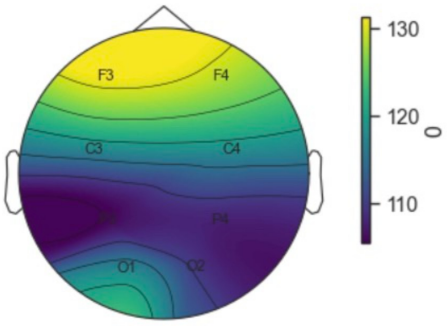
Sleep in HD—Quantitative EEG Analysis

Sleep in Huntington's Disease is increasingly being studied because of growing evidence of sleep changes in HD patients, as well as evidence that suggests that treating sleep early on in the disease may improve cognitive and motor outcomes, and even slow down disease progression (see page 10).

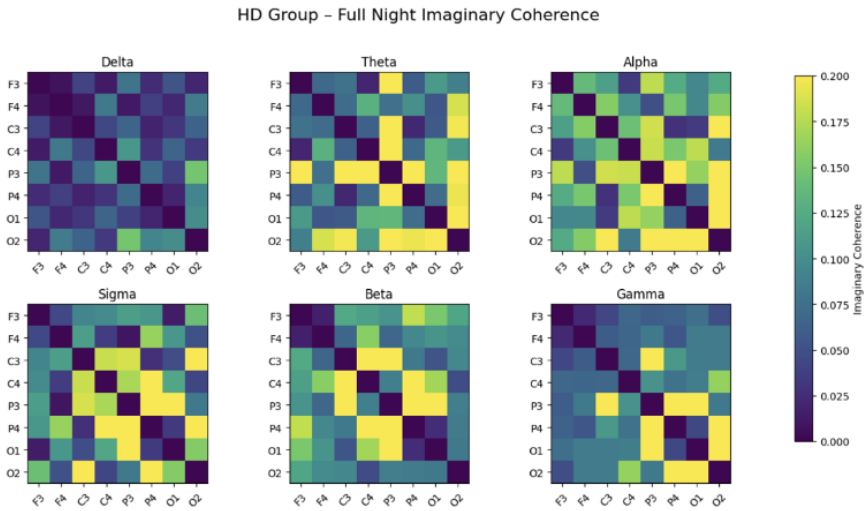
Over the past 12 years, we have collected data in an EEG study, where participants spent the night in a sleep lab or a home setup with EEG sensors attached to their scalp. These sensors record the brain's electrical activity, or brain waves, while the person sleeps. Afterward, we analyse the brainwaves to look for patterns, during different stages of sleep (light sleep, deep sleep, REM sleep). We can also measure how stable these patterns are, which can give insights into sleep quality and health.

Our aim is to track how sleep physiology changes through disease progression from pre manifest to manifest stages compared to control subjects who don't have HD. These findings will help us identify what processes in the brain we have to target, and guide us in developing new sleep-based therapies.



Topographical map showing the spatial distribution of electrical activity in the brain during deep (slow wave) sleep in HD participants.

The electrical activity is measured in power (or strength of the signal from the brain), measured in microvolt squared as shown on the image above.



Heatmap showing connectivity between EEG electrodes in different regions, which shows how well different parts of the brain are communicating with each other in HD.

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DOPA-HD

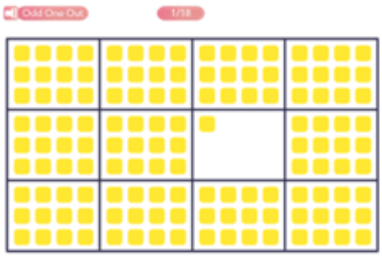
Funded by NIHR Biomedical Research Centre – Dementia theme

DOPA-HD focuses on the role of the brain chemical dopamine, which is known to play an important role in coordinating movements as well as helping with certain aspects of thinking such as memory, attention, and planning. We know that dopamine contributes to some of the motor features of HD, as we use drugs in the clinic to block its action as a way to treat the chorea of HD. However, we do not know how these drugs affect the way people with HD think.

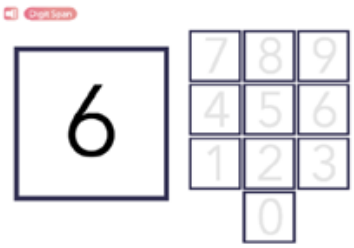
DOPA-HD investigates the immediate effects of increasing and decreasing levels of brain activation by dopamine on cognition in HD. During DOPA-HD, participants visited our centre on four separate occasions during which they took one of the following: a drug which activates the dopamine receptor (effectively increasing dopamine levels), a drug that blocks the effects of dopamine (effectively decreasing dopamine levels), both drugs taken at the same time (effectively producing no changes in dopamine levels), or a placebo. After a break of 90 minutes, participants undertook some computer based cognitive tasks.

The trial completed recruitment in August 2024 and a huge thank you to everyone who participated! We hope to provide an update on the results of the trial in the near future as Luke joined the group for a few months this year and has taken on the data analysis.

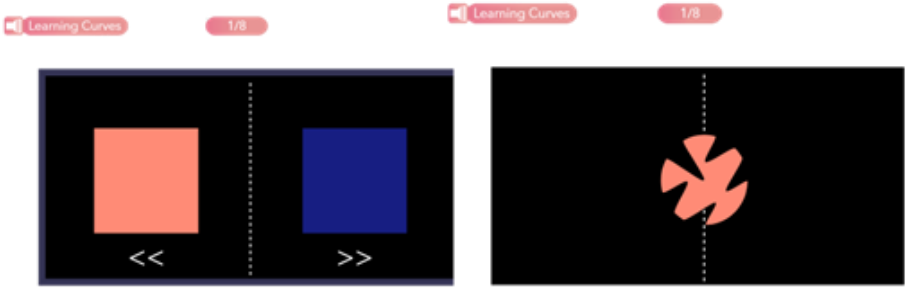
If you would like to hear more about this study, please contact Amy on ahe28@cam.ac.uk or 01223 747489.



Odd one out test used as part of the cognitive battery



Digit span task used as part of the cognitive battery



Paired associate learning task used as part of the cognitive battery

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Social functioning in Huntington's Disease

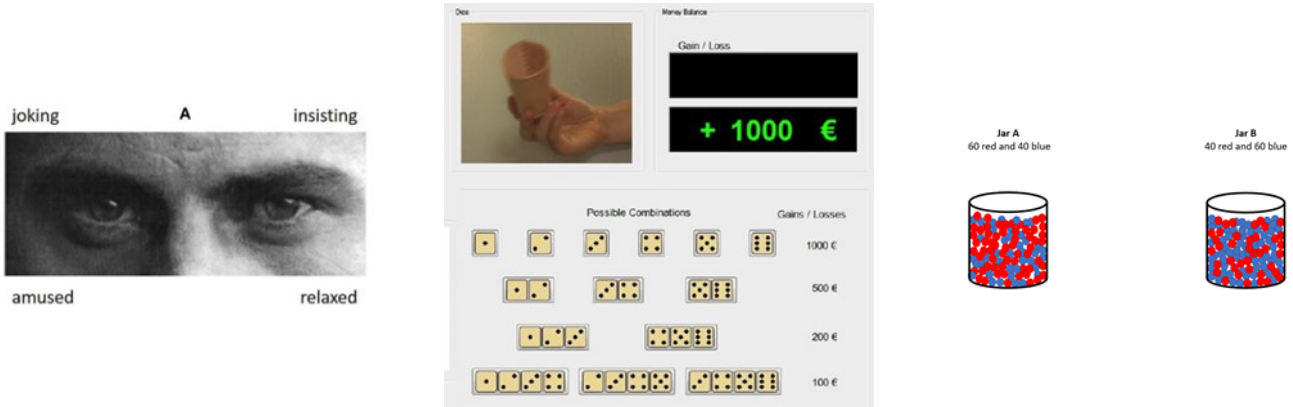
Over the past 4 years we have completed multiple projects aiming to better understand social functioning in individuals with Huntington's Disease. Social functioning refers to how well a person manages daily life and relationships. It includes their ability to work, maintain friendships, take care of themselves, and handle responsibilities.

The first project explored how thinking difficulties and mental health symptoms relate to problems with social interactions in HD. The study examined various cognitive skills that might be connected to social functioning, including understanding emotions, decision-making, self-control, and motivation. The findings showed that people in the early stages of HD struggle with social understanding and self-control. Additionally, reduced motivation to engage with social cues appeared to contribute to social understanding difficulties.

The second project aimed to gain a deeper understanding of how everyday social interactions are affected in HD. To assess social functioning, participants and their close companions completed questionnaires and a lie detection task. The results showed that companions of individuals with HD were more likely to report social difficulties than the affected individuals themselves. Further HD participants showed a reduced ability in detecting lies accurately.

The final project focused on social isolation and loneliness as either could be outcomes of poor social functioning. It was found that people with HD were more likely to be socially isolated without feeling lonely, which was linked to a reduced interest in social interactions. In contrast, individuals with Parkinson's Disease often felt both socially isolated and lonely, with loneliness linked to their perception of social difficulties.

Overall, these projects showed that HD is associated with a change in social functioning and that these problems seem to be related to reduced motivation.



A screenshot of some of the assessments participants are asked to complete on the Social Decision making study

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EYE-HD: Can we study the back of the eye to track disease progression in HD?

We are exploring whether there are subtle but measurable abnormalities in eye function in Huntington's disease (HD). While HD is known to involve an abnormal protein present in every cell of the body (mutant huntingtin), this study focuses specifically on the anatomy of the retina and its changes over time in individuals with HD. Importantly, patients with HD typically do not experience poor vision, so we are looking for very subtle abnormalities that could provide new insights.

To investigate this, Dimitri employed a non-invasive imaging technology called Optical Coherence Tomography (OCT). OCT uses light to capture detailed, micrometer-level images of the retina, allowing us to investigate whether potential changes may be seen in HD patients.

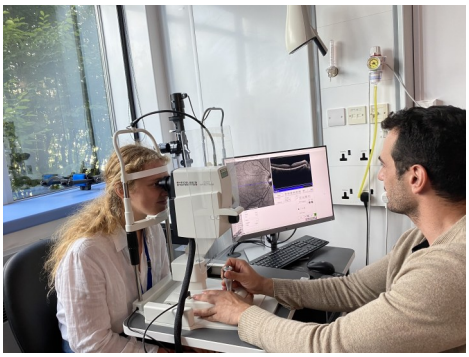
In addition to studying retinal anatomy, an MPhil student who joined us for 1 year, Clara, investigated a phenomenon called fixation loss—an impaired ability to focus on a stationary target, such as the tip of a pen, for an extended period. While healthy individuals can maintain their gaze on a target without difficulty, we suspect that HD patients may experience minor, involuntary eye movements that divert their eyes away from the target.

An interim analysis has revealed that fixation loss may help identify HD carriers who are closer to manifesting the disease. This is an exciting development, but more work is needed to confirm these findings. As a result, Will, who has now taken the study on, is recruiting more participants to explore all this in greater detail.

The ultimate goal is to bring this technology into clinical practice to aid earlier diagnosis and better monitor disease progression.

Participation in this study involves visiting the hospital campus for clinical and eye assessments at a specialised facility located near the clinic. The eye assessments are similar to those performed during a standard optician's annual eye exam and are entirely non-invasive.

If you are eligible, you may be approached about participating during your clinic appointment.



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Fluid Biomarkers in HD

This work has been made possible from a donation from an HD family—thank you!

You might remember from the last newsletter that we had a student called Nat Owen. Her project with us was to look at whether various blood proteins might help to predict how close an HD gene carrier is to becoming symptomatic of HD. This is important not only for individuals, who may want to know this information, but also for making participant recruitment to clinical trials more accurate.

Some other studies had suggested a few candidate bloods proteins, but one of the main bottlenecks stopping them being used was the fact that there had been no study of how they behave over a long time period - especially in the run up to HD becoming manifest.

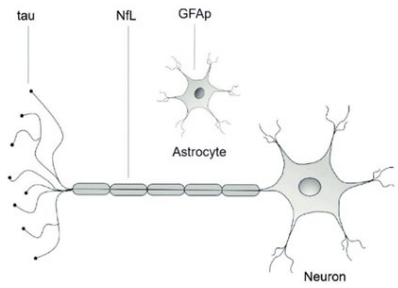
So this is what we did – using samples from the last 14 years, collected as part of our observational sleep study. We're delighted to report that we had a strong positive result for one of the proteins, known as neurofilament-light or 'NfL'. This result has now been published – if you'd like to know more, here is a link to the paper, and a link to a summary on Twitter:

https://tinyurl.com/32t38suv

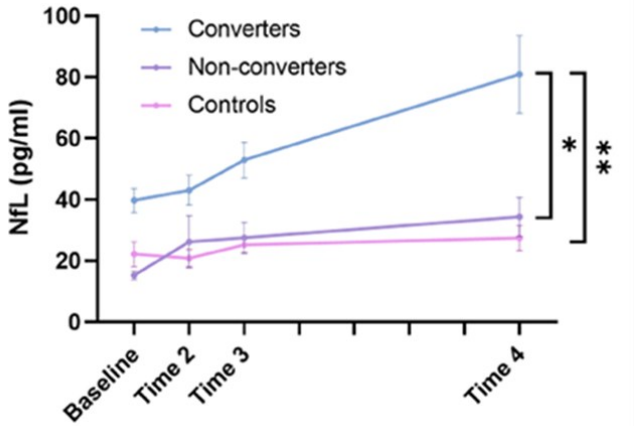
https://tinyurl.com/5zrjn5wj

While this blood test can't yet be used in clinical practice, we hope that this study will hasten its adoption into clinical practice.

A huge thank you to all the sleep study participants who took part in this sub-study!



Types of fluid biomarkers from neurons and astrocytes (type of glial cell)



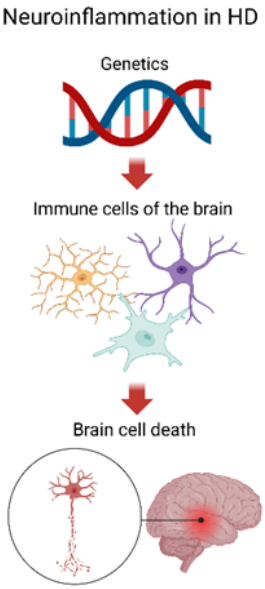
Graph from our recent publication shows how blood neurofilament levels changed over 14 years in HD gene carriers and controls. Levels were stable in pre-symptomatic carriers but rose earlier and faster in those within 14 years of symptom onset. This blood test could help predict disease onset, though larger studies are still needed.

HUNTINGTON'S DISEASE NEWSLETTER

John Van Geest Centre for Brain Repair & Addenbrookes Hospital

Jumping genes in HD

A fascinating but underexplored player in Huntington's disease (HD) could be transposable elements (TEs)—segments of DNA that can "jump" within the genome. Some TEs originated from ancient viral infections that integrated into our ancestors' DNA. Over millennia, our bodies have evolved mechanisms to suppress these elements, effectively "silencing" them. However, during diseases like HD, these ancient viral sequences may reawaken. Our immune system, designed to combat viral threats, can mistake reactivated TEs for invaders and trigger an inflammatory response, potentially causing further harm.



In collaboration with Johan Jakobsson's team in Lund, Sweden, our lab previously linked TEs to inflammation in Parkinson's disease. Building on this discovery, we are now investigating whether the same process occurs in HD.

Sophie, a second-year PhD student, is using next-generation sequencing on HD patient brain tissue to determine if TEs are reactivated and linked to the neuroinflammation seen in HD brains. The ultimate goal is to understand how "jumping genes" could be targeted for innovative HD therapies. She looks forward to sharing her findings in the next newsletter!

The Cambridge Brain Bank

You are probably familiar with organ donations of the heart, kidneys or liver to sustain the health or even the life of people in need. Brain donation for research is a precious and unique gift. Scientists can learn and understand more about disease processes when they are able to work on donated tissue. The donation of a brain and other parts of the nervous system is a big decision and needs much discussion. Advice is available from the Cambridge Brain Bank team who would be very happy to talk through any concerns you or your family may have.

You can contact the team on 01223 217336 or email add-tr.cambridgebrainbank@nhs.net for further information as well as visiting the website: https://www.cuh.nhs.uk/our-research/get-involved/donate-body-to-medical-science/

Over the last 8 years we have had 13 donations from HD patients. We would like to thank the patients and their families for this.

HUNTINGTON'S DISEASE NEWSLETTER

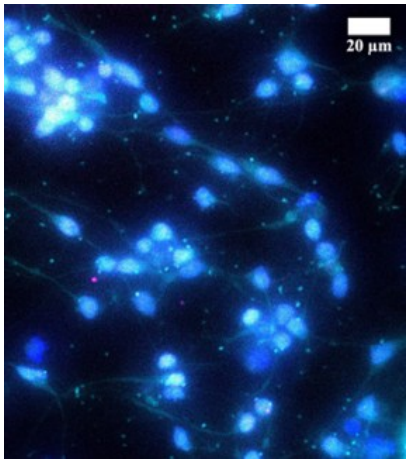
John Van Geest Centre for Brain Repair & Addenbrookes Hospital

Using stem cells to understand jumping genes in HD

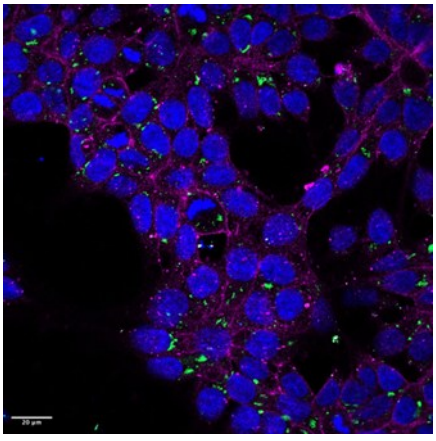
The Huntington's disease mutation is a lengthening of a triplet of DNA bases (CAG) in the Huntingtin gene, known as an expansion. This expansion can become longer, both between patient generations, but also during a patient's life in specific brain cells. What drives this expansion, and what makes specific brain cells more vulnerable to this process, is not fully understood, but it is thought that longer repeats cause more problems for the cells.

One theory is that specific brain cells in Huntington's have activation of a part of their genome called transposable elements, also known as jumping genes (see page 16). Jumping genes when activated can move places in your genome. They are known to cause genome damage and make the genome unstable, therefore they could make the Huntington's mutation worse by greatly increasing the CAG repeat length.

The first part of this lab-based project involves growing the brain cell most affected in Huntington's, the striatal medium spiny neurons. This has been done using stem cells with and without the Huntington's CAG expansion. The next part of my project will involve genetic editing of the neurons to activate jumping genes, and measuring the Huntington's mutation before and after editing, to see if activating jumping genes has any effect on the Huntington's mutation.



Picture no 1: Striatal medium spiny neurons (brain cells affected most in Huntington's disease) grown from stem cells in a dish



Picture no 2: Transposable elements (jumping genes, green dots) in a Huntington's patient stem cell line

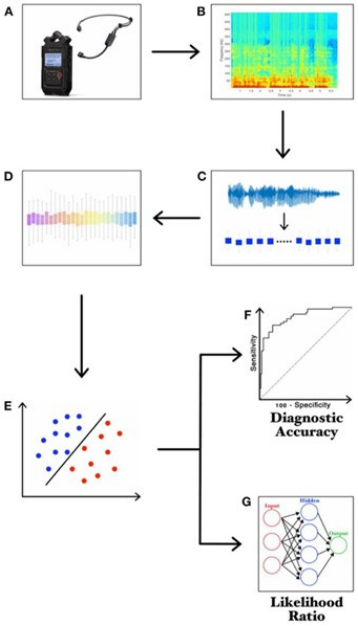
HUNTINGTON'S DISEASE NEWSLETTER

John Van Geest Centre for Brain Repair & Addenbrookes Hospital

Voice analysis in HD

Funded by Sapienza University of Rome

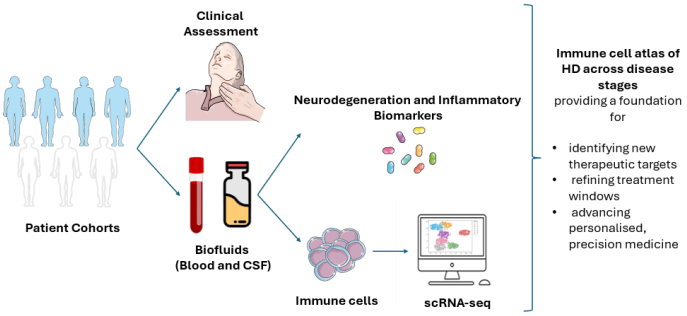
Chiara joined the Barker Lab for three months in 2025 to work on *Voice-HD*, a project investigating speech alterations in Huntington's disease (HD). Conducted as part of her medical degree at the Sapienza University of Rome under supervision from Professor Antonio Suppa and Dr. Martina Patera, the study explores how HD affects speech, which is impaired in nearly 90% of patients. Early signs include reduced fluency and clarity, worsening over time. Since symptoms vary across individuals, understanding these patterns is key for early diagnosis and disease monitoring. Chiara has been collecting clinical data—including motor, cognitive, and psychiatric assessments—alongside voice recordings of patients performing tasks like sustained vowels and sentence reading. These will be analysed using AI to identify distinguishing features and compare them with healthy controls. The goal is to develop non-invasive, AI-based tools that use voice as a biomarker to support earlier diagnosis and improve clinical management of HD.



Workflow for voice analysis: (A) recording; (B) spectrogram; (C) feature extraction; (D) selection; (E) classification; (F) ROC analysis; (G) likelihood ratios via ANN. Adapted from Suppa et al., Frontiers in Neurology (2022).

The immune system and HD

In this joint project between the Barker and Jones labs, Bristena will join our group to work on a project using single-cell RNA sequencing (scRNA-seq) to investigate how the immune system influences the progression of Huntington's disease (HD). While HD is primarily known for neurodegeneration, immune changes are increasingly recognised as key contributors. We will collect blood and cerebrospinal fluid (CSF) samples from participants across all disease stages and healthy controls to map immune cell populations and their gene activity at single-cell resolution. By comparing peripheral and central immune profiles and linking them to clinical assessments and biomarkers like neurofilament light chain (see page 15) and cytokines, we aim to identify stage- and region-specific immune signatures. We will also explore the role of transposable elements (see page 17) in neuroinflammation and integrate findings with single-nucleus RNA sequencing of postmortem brain tissue to study immune cell infiltration. This work aims to create the first comprehensive immune cell atlas of HD, guiding future therapies and precision medicine approaches.



Immune cell atlas of HD across disease stages

HUNTINGTON'S DISEASE NEWSLETTER

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Recent publications

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Voysey, Z. J., Goodman, A. O. G., Rogers, L., Holbrook, J. A., Lazar, A. S., & Barker, R. A. (2025). Sleep abnormalities are associated with greater cognitive deficits and disease activity in Huntington's disease: a 12-year polysomnographic study. *Brain Communications*, *7*(2), fcaf126. https://doi.org/10.1093/braincomms/fcaf126

HUNTINGTON'S DISEASE NEWSLETTER

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Websites of interest

You can find more information on our new website!

https://www.barkerlab.group.cam.ac.uk/

@thebarkerlabgroup.bsky.social

Barker Williams-Gray Lab

https://en.hdbuzz.net/

https://www.hda.org.uk/

Huntington's disease youth organisation

https://en.hdyo.org/

Donations

If you would like to donate to any of our research projects, please contact Katie Andresen on kera2@cam.ac.uk or 01223 331141

You can write to us at the below address: John Van Geest Centre for Brain Repair, E.D. Adrian Building, Forvie Site, Robinson Way, Cambridge, CB2 0PY