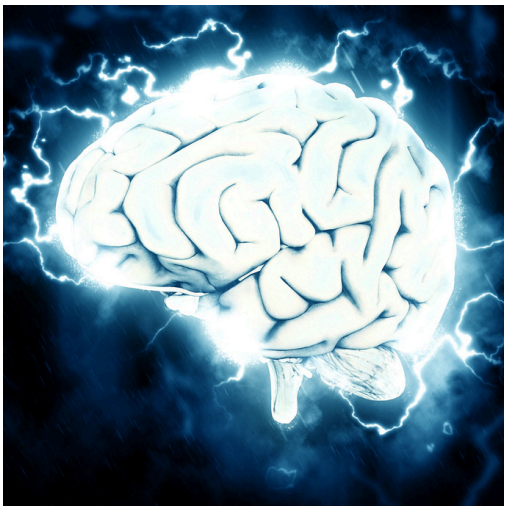
EHDN

iWG Newsletter

Edition 4 | October 2025

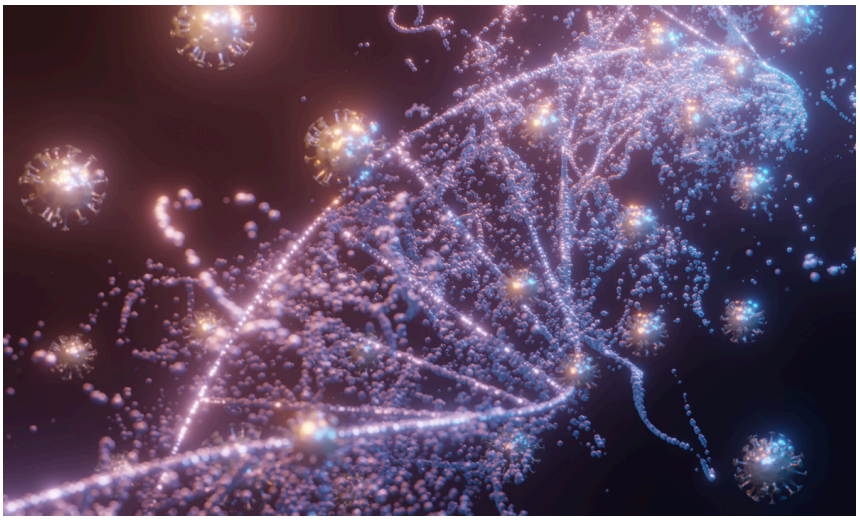


Dear reader...

Welcome to the fourth edition of the **Imaging Working Group (iWG) newsletter!**
This newsletter provides **updates on imaging studies**, **advancements** and **techniques** in **neuroimaging** that are enhancing our understanding of HD. Whether you are a researcher, clinician or someone impacted by HD, our goal is to **keep you informed and inspired** by the progress being made in this field!

Would you like to be featured?
Please email:
m.leocadi@ucl.ac.uk

Landmark results from the AMT-130 trial (UniQure)



September 24th, 2025, will certainly be remembered as an **historic day for HD**.
UniQure announced **"positive topline results"** from their pivotal **phase I/II trial of AMT-130**, the **first gene therapy tested in HD**.
This therapy is delivered through a highly complex neurosurgical procedure, **stereotactic surgery**, where tiny catheters are guided into the correct brain regions using **live MRI imaging**.

The trial met its primary endpoint, with high-dose AMT-130 showing a remarkable **75% slowing of disease progression based on cUHDRS after 36 months** compared with controls. It also **met its secondary endpoint**, demonstrating **slowing of functional decline** as measured by TFC. In addition, **mean CSF NfL levels were below baseline after 36 months**.

This marks the **first time a drug has been shown to alter the course of HD** in a clinical trial.
While the findings **must be interpreted with some caution**, they represent **a truly monumental moment** for the entire HD community.

Cell-specific mechanisms drive connectivity across the time course of Huntington's disease

We are delighted to highlight a recent publication in Nature Communications led by our iWG member **Carlos Estevez-Fraga.**

The study was carried out under the joint supervision of **Peter McColgan (Roche)** and **Sarah Tabrizi (UCL)**, with contributions from multiple international research centers, including **McGill University (Canada)** and **Cambridge University (UK)**.

Using **Morphometric INverse Divergence (MIND)**, the researchers combined data from **three large datasets** comprising more than **500 individuals with HD and controls**. This allowed them to examine connectivity changes spanning over two decades before the onset of symptoms through to the early stages of functional decline.

Remarkably, the study revealed that **individuals with HD exhibit stronger brain connections as early as 22 years before motor onset** compared with controls. Strikingly, these increased connections undergo **sharp declines as the disease advances**, a process linked to **elevated neurofilament light protein**, indicating underlying neuronal loss.
The team also demonstrated that these **connectivity differences are associated with** neurotransmitters such as **acetylcholine and serotonin**, particularly in deep cortical layers.


Carlos-Estevez Fraga (left) and Peter McColgan (right)

Carlos Estevez-Fraga is a **neurologist** and **researcher** working at **Roche** since 2024, where he aims to develop **new treatments** for rare neurological diseases.
He previously was a **Senior Clinical Research Fellow** with Sarah Tabrizi at **UCL**, where he stayed between 2018 and 2024, completing **his PhD in imaging biomarkers**, doing Huntington's clinics, and as clinical trial lead until he moved to the pharmaceutical industry.

Peter McColgan is a **neurologist** with over 10 years experience in **HD**. He is a **Global Development Leader** and **medical director** for HD programs at **Roche**. He previously was an **Assistant Professor** in **Neurology** at UCL HD Centre. His **PhD** focused on brain networks in pwHD using MRI. He also completed post-doc training in 7T MRI ultra-high resolution brain imaging.

Reference

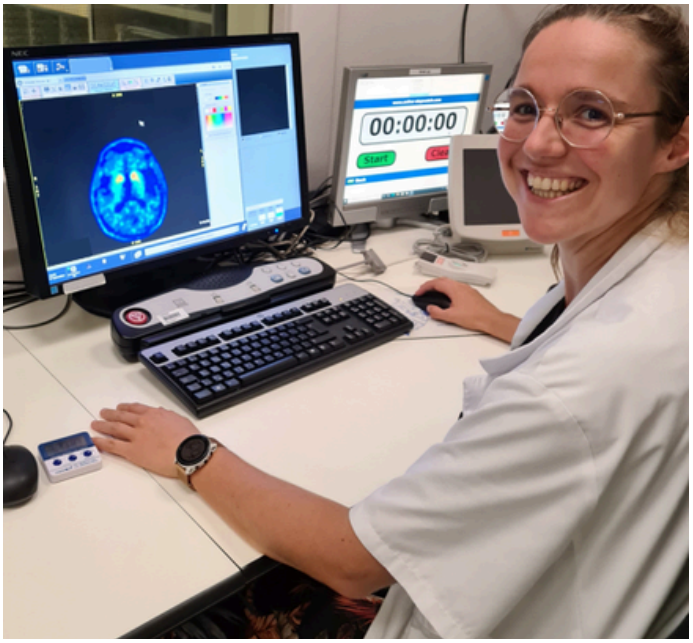
Estevez-Fraga, C., Sebenius, I., Hansen, J.Y., Hänisch, B., Zeun, P., Scahill, R.I., Gregory, S., Johnson, E.B., Wild, E.J., Byrne, L.M., Durr, A., et al., 2025. Cell-specific mechanisms drive connectivity across the time course of Huntington's disease. Nature Communications, 16(1), p.5519.
https://doi.org/10.1007/s00259-025-07394-w

PET imaging with [^{11}C]CHDI-00485180-R, designed as radioligand for aggregated mutant huntingtin, in people with Huntington's disease

In this edition, we are pleased to feature a new publication from **Aline Delva**, one of our iWG members, on the **iMagemHTT study**.

The study evaluated the **novel PET radioligand [^{11}C]CHDI-00485180-R ([^{11}C]CHDI-180R)**, developed to image aggregated mutant huntingtin (mHTT) in people with HD. Following encouraging results in HD mouse models and healthy volunteers, dynamic [^{11}C]CHDI-180R PET scans with arterial sampling were performed in 12 people with manifest HD and 12 healthy controls (6 age-matched and 6 younger participants), using MRI-based segmentation and kinetic modeling to calculate **total distribution volumes (V_T)** and **distribution volume ratios relative to cerebellum (DVR_{CBL})**.

While V_T values showed high interindividual variability and did not differ significantly between groups, **[^{11}C]CHDI-180R DVR_{CBL} values** were **significantly higher** in **frontal, temporal, parietal, and occipital cortices** in HD. These findings suggest that [^{11}C]CHDI-180R PET, with the cerebellum as a pseudo-reference region, may enable in vivo detection of regional mHTT aggregates in HD.
In summary, although [^{11}C]CHDI-180R has limitations as a first-generation PET tracer for quantifying mHTT aggregates in the human brain, this study represents the **first attempt to visualise and measure these aggregates in vivo**.



Aline Delva

The findings underscore the need to develop second-generation radioligands that can address the limitations of [^{11}C]CHDI-180R.

Aline Delva is a junior staff neurologist at the **University Hospitals Leuven Belgium**, within the Movement Disorders and Cognitive Neurology programs.
She is a research fellow at the **Laboratory for Parkinson Research at KU Leuven** and finished her clinical-research fellowship in Movement Disorders at McGill University Montreal Canada last year.
Her research focuses on **imaging** and **fluid biomarkers** in Huntington's disease and synucleinopathies.

Reference

Delva, A., Koole, M., Serdons, K., Bormans, G., et al., 2025. PET imaging with [^{11}C] CHDI-00485180-R, designed as radioligand for aggregated mutant huntingtin, in people with Huntington's disease. European Journal of Nuclear Medicine and Molecular Imaging, pp.1-11. https://doi.org/10.1007/s00259-025-07394-w

Congratulations to Eva Woods for being one of the HDBuzz Prize for Young Science Writers winners!

In this fourth edition, we are very pleased to announce that one of our iWG members, **Eva Woods**, is amongst the **winners of the HDBuzz Prize for Young Science Writers**, which was sponsored by the **Huntington's Disease Foundation (HDF)**.

Her winning piece, **"Calm before the storm: early clues of HD found in brainwaves"**, refers to a study (Delussi et al., Clinical Neurophysiology 2024) where **EEG**, a painless method to record brainwaves, was used to record how the brain automatically reacts to unexpected sounds. This brain signal, called **mismatch negativity (MMN)**, reflects the brain's ability to detect change even without conscious attention.

In the study, people with HD who showed symptoms had **weaker MMN responses**, suggesting a **reduced automatic "surprise detector"**. On the other hand, **pre-symptomatic HD people showed no reduction in MMN size**, but instead **greater timing consistency (theta phase coherence)**.

This may represent a compensatory mechanism, where the brain works harder to keep things in sync before symptoms appear.

Eva Woods

Although the study was small and brainwave changes did not directly match traditional symptom measures, the findings suggest **EEG could provide a simple, non-invasive way to detect and monitor HD's earliest effects**. With its ease of use and potential for at-home application, EEG may one day become a valuable tool for tracking disease progression long before visible symptoms emerge.

Eva is currently a **PhD student** at **Trinity College Dublin**, where her research combines **MRI, EEG and TMS** to identify **early brain changes** in people with HD.

Reference

Delussi, M., Valt, C., Silvestri, A., Ricci, K., Ladisa, E., Ammendola, E., Rampino, A., Pergola, G. and de Tommaso, M., 2024. Auditory mismatch negativity in pre-manifest and manifest Huntington's disease. Clinical Neurophysiology, 162, pp.121-128.
https://doi.org/10.1016/j.clinph.2024.03.020

Looking ahead

We encourage you to **share your ongoing projects**, recent **publications**, and **ideas** for **future collaborations**.
Your contributions are the **foundation** of this group, and we look forward to featuring your work in upcoming editions.
We want this newsletter to be **a collaborative space**! If you have updates, publications, imaging results or job opportunities you would like **to share** with the community, please reach out.
Together, we can amplify the incredible work happening in this community.
On behalf of the iWG, THANK YOU for your commitment to advancing imaging research and for being part of this vibrant community.

Warm regards,

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