EHDN

iWG Newsletter

Edition 3 | July 2025

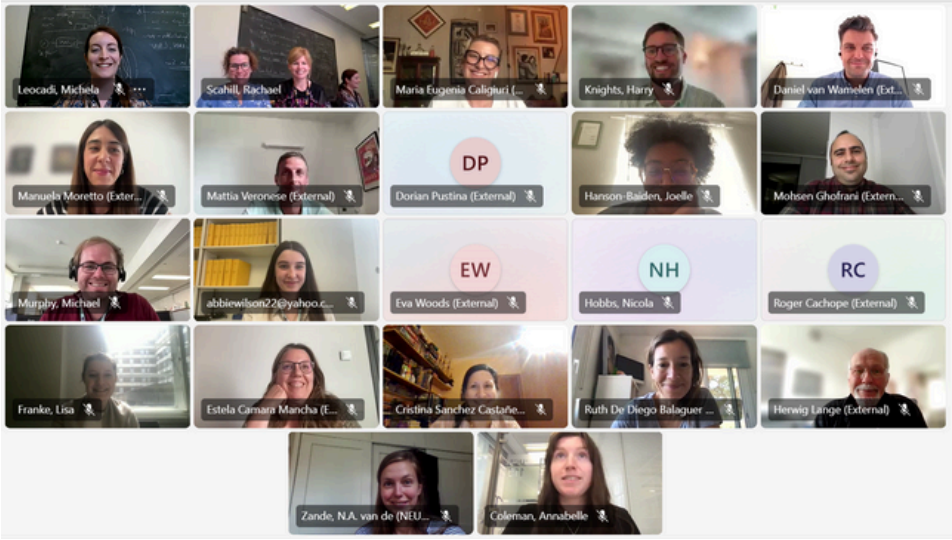
Dear reader...

Welcome to the third 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

Remote EHDN Imaging Working Group meeting, June 9th 2025



Our **remote iWG meeting** took place on June 9th, and we had over 20 members of our WG joining the meeting from the UK, US, Australia, Italy, Spain, Ireland, Netherlands and Germany. Our agenda for the day was:

- **Nicola Hobbs & Rachael Scahill,**
  University College London
  Welcome
- **Audrey E. De Paepe,**
  Columbia University
  Mapping apathy in HD with multimodal neuroimaging (page 2)
- **Daniel J van Wamelen & Manuela Moretto**
  King's College London & University of Padua
  An update on the iMarkHD study
  (featured in our March edition)
- **Maria Eugenia Caligiuri,**
  University "Magna Graecia" of Catanzaro
  Hybrid PET/MRI uncovers distinct morphological and metabolic traits in paediatric and adult-onset HD (page 3)
- **Michela Leocadi,**
  University College London
  iWG newsletter update

Mapping apathy in Huntington's disease with multimodal neuroimaging

Audrey E. De Paepe (center) at her PhD defense (University of Barcelona). Supervisors include Dr. Estela Camara (second from left), Dr. Alexia Giannoula (left), and Dr. Ruth De Diego (right). The PhD Committee includes, from remaining left to right, Dr. Carles Soriano Mas, Dr. Rachael Scahill, and Dr. Javier Pagonabarraga.

We are delighted to report that **Audrey De Paepe**, one of our iWG members, recently defended her PhD at the University of Barcelona.

The focus of Audrey's work was to demonstrate that **cognitive and auto-activation deficits** are the most severe forms of **apathy** in HD, and each are represented by distinct cortico-striatal tracts.
Her research showed that **increases in apathy** were related to **reductions in grey matter volume** in the **middle cingulate cortex**, and also that initial volume in this region was able **to predict changes in apathy** over time in a longitudinal study (1).

Further work (2) indicated that **lifelong cognitive engagement** (e.g., learning languages, playing an instrument) is linked with **slower progression of cognitive, motor, and psychiatric outcomes in HD inviduals.**

Audrey is currently in her final year at the Columbia University Vagelos College of Physicians & Surgeons. She plans to pursue neurosurgery, and it is her mission to advocate for clinical trials for people living with HD.

References

1. De Paepe, A.E., Ara, A., Garcia-Gorro, C., et al., 2021. Gray matter vulnerabilities predict longitudinal development of apathy in Huntington's disease. Movement Disorders, 36(9), pp.2162-2172. https://doi.org/10.1002/mds.28638
2. De Paepe, A.E., Plana-Alcaide, Y., Garcia-Gorro, C., et al., 2024. Cognitive engagement may slow clinical progression and brain atrophy in Huntington's disease. Scientific Reports, 14(1), pp.1-16. https://doi.org/10.1038/s41598-024-76680-8

Pediatric Huntington's disease brains have distinct morphologic and metabolic traits: the RAREST-JHD study



From left: Maria Eugenia Caligiuri, Umberto Sabatini and Ferdinando Squitieri

In this new edition, we are delighted to feature a recent study led by **Maria Eugenia Caligiuri** and **Umberto Sabatini** from **University Magna Graecia in Catanzaro**, **Italy**, in collaboration with **Ferdinando Squitieri** from **Fondazione Lega Italiana Ricerca Huntington (LIRH)** and **IRCCS Casa Sollievo della Sofferenza** in **San Giovanni Rotondo**, **Italy**.

The work stems from the **RAREST-JHD study**, investigating pediatric-onset Huntington's disease **(POHD)**, a rare and severe form of HD associated with ≥60 CAG repeats (1).
By using **simultaneous [18F]FDG-PET/MRI**, authors were able to observe that **POHD brains** exhibited **significantly greater atrophy and hypometabolism** in the **striatum**, as well as distinctive **alterations in cortical and thalamic glucose metabolism** compared to adult-onset HD **(AOHD)** with comparable clinical severity and disability.

Despite the more severe striatal damage, **POHD** showed relatively **preserved cortical thickness**, in line with histopathological findings (2,3).

A **POHD subgroup** who was followed-up longitudinally revealed **more dynamic regional changes in FDG uptake** and **faster yearly volume loss**, particularly in **parietal**, **occipital**, and **caudate regions**.

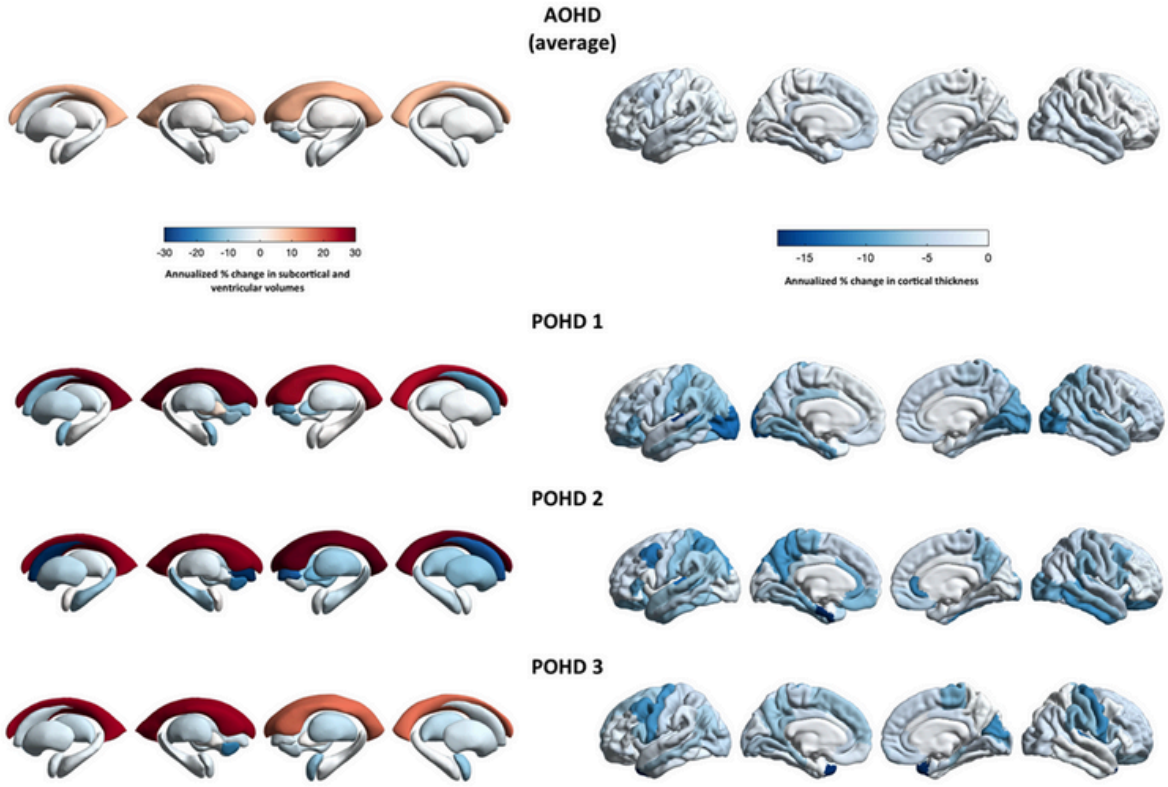
Results of this study interestingly highlights the presence of **thalamic hypermetabolism**, which may play a role in compensatory mechanisms in POHD, despite striatal neurodegeneration.

These findings support the hypothesis that **POHD** represents a HD subtype with **distinct characteristics from AOHD**, including large, unstable CAG repeats and **region-specific tissue vulnerability**.
The study highlights the importance of dedicated biomarkers and disease models for POHD, to capture its pathophysiology and progression.

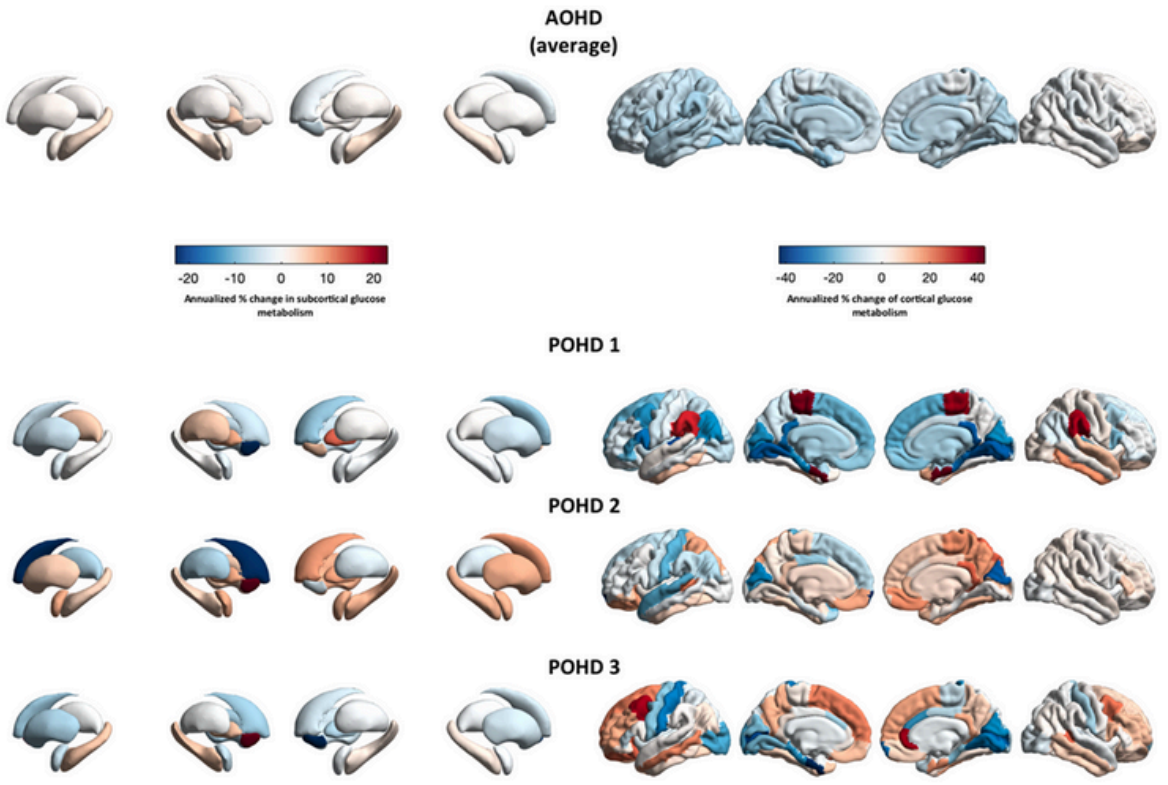
References

1. Caligiuri ME, et al., 2024. Pediatric Huntington disease brains have disticnt morphologic and metabolic traits: the RAREST-JHD study. Mov Dis Clin Pract. Dec;11(12):1592-1597. https://doi.org/10.1002/mdc3.14223
2. Fusilli C, et al., 2018. Biological and clinical manifesta- tions of juvenile Huntington's disease: a retrospective analysis. Lancet Neurol;17:986–993. https://doi.org/10.1016/s1474-4422(18)30294-1
3. Tramutola A, et al., 2023. GLUT-1 changes in paediatric Huntington disease brain cortex and fibroblasts: an observational case- control study. EBioMedicine;97:104849. https://doi.org/10.1016/j.ebiom.2023.104849

Pediatric Huntington's disease brains have distinct morphologic and metabolic traits: the RAREST-JHD study



This figure (above) shows annualised percentage rate of morphological changes in the AOHD cohort (averaged from six patients) and individual POHD patients



This figure (above) shows annualised percentage rate of changes in glucose uptake in the AOHD cohort (averaged from six patients) and individual POHD patients

Bias in HD-ISS staging introduced by the FreeSurfer cross-sectional stream: Insights from the Huntington's Disease Young Adult Study (HD-YAS)

Harry Knights is a **Clinical Research Fellow** working at the **Huntington's Disease Centre at UCL**, and he will soon be starting his PhD exploring PDE10A-PET signal as a potential clinical trial biomarker in far-from-onset HD.

Harry is the **lead author** of a paper currently under review in the Journal of Huntington's Disease, investigating the **impact of using FreeSurfer on HD-ISS staging**. As the HD-ISS system is expected to serve as inclusion criteria in future clinical trials, this work has important implications.

The **FreeSurfer software** offers both **cross-sectional and longitudinal processing streams**. For individuals with multiple MRI scans, the longitudinal stream creates a within-subject template to enhance segmentation accuracy. In contrast, the cross-sectional stream processes each scan independently. For participants with only one MRI scan, the longitudinal stream cannot be used, and segmentation must rely on the cross-sectional stream.

HD-ISS Stage 1 cut-offs were originally derived using the **longitudinal stream** to optimise accuracy. However, **upcoming clinical trials** will likely need to stage participants based on **a single MRI**, making the cross-sectional stream more relevant in this context.

It is already known that striatal volumes and HD-ISS staging are sensitive to the choice of software and version.

Harry Knights

In this short communication, Harry and colleagues used **baseline data from the HD-YAS study** to assess the **bias** introduced by switching from the longitudinal to the cross-sectional FreeSurfer stream.

Their analysis revealed that the **cross-sectional stream yields smaller caudate and putamen volumes**, which in turn shifts some individuals **from HD-ISS Stage 0 to Stage 1**. These findings underscore the need for stream-specific cut-offs to be developed before applying HD-ISS criteria in clinical trial settings.

References

1. Scahill, R. I., et al., 2020. Biological and clinical characteristics of gene carriers far from predicted onset in the Huntington's disease Young Adult Study (HD-YAS): a cross-sectional analysis. The Lancet Neurology, 19(6), 502-512. https://doi.org/10.1016/s1474-4422(20)30143-5

Run4HDYO 5K walk/run benefitting the Olivia (Liv) Martinez Scholarship Fund

On Saturday, **June 28th**, several members of the **iWG**, alongside friends from the **HD Centre UCL**, the **HD Youth Organisation (HDYO)**, and the wider **HD community**, met up in **Battersea Park**, London, to **run/walk 5K** to raise awareness on HD and funds benefitting the **Olivia (Liv) Martinez Scholarship Fund**.
This scholarship has been created in memory of Liv, an HDYO ambassador whose passion, kindness, and strength touched so many lives.
The money raised (**more than £2700** at the time of writing) will help fund future scholarships which will enable young individuals impacted by HD from all over the world to be able to attend the next **HDYO congress in 2027**.

There is still time to donate if you can: click here

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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