EHDN

iWG Newsletter

Edition 2 | March 2025

Dear reader...

Welcome to the second 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!

Highlights from the International Young Adult (HDYO) Congress in Prague, Czech Republic

Prague Astronomical Clock and Church of Our Lady before Týn

Earlier this month (March 14th-16th), the **HDYO Congress** was held in the beautiful city of **Prague,** showcasing an incredible example of **partnership** and **collaboration** within the HD community. Attendees included young people impacted by HD, researchers, scientists from pharmaceutical companies, mental health professionals and various other experts. This congress served as a powerful reminder that **through collaboration,** we can all achieve **remarkable progress** - and this is what we strive for in our iWG!

We welcome **new contributions** for the next editions!
Please get in touch:
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Longitudinal increase in somatic expansion ratio is a significant predictor of early striatal loss: insights from the HD-YAS study

HD-YAS team. From left: Michela Leocadi, Rachael Scahill, Mena Farag, Lisa Franke, Henrique Nascimento, Olivia Thackeray, Nicola Hobbs.

In January 2025, the latest work from the **HD Young Adult Study (HD-YAS)** team, led by **Prof. Sarah Tabrizi** from the **HD centre at University College London (UK)** was published in the journal of **Nature Medicine.**

The aim of the study is to determine changes in **early disease signs;** this will help guide any potential future disease-modifying treatments and design preventative treatment trials.

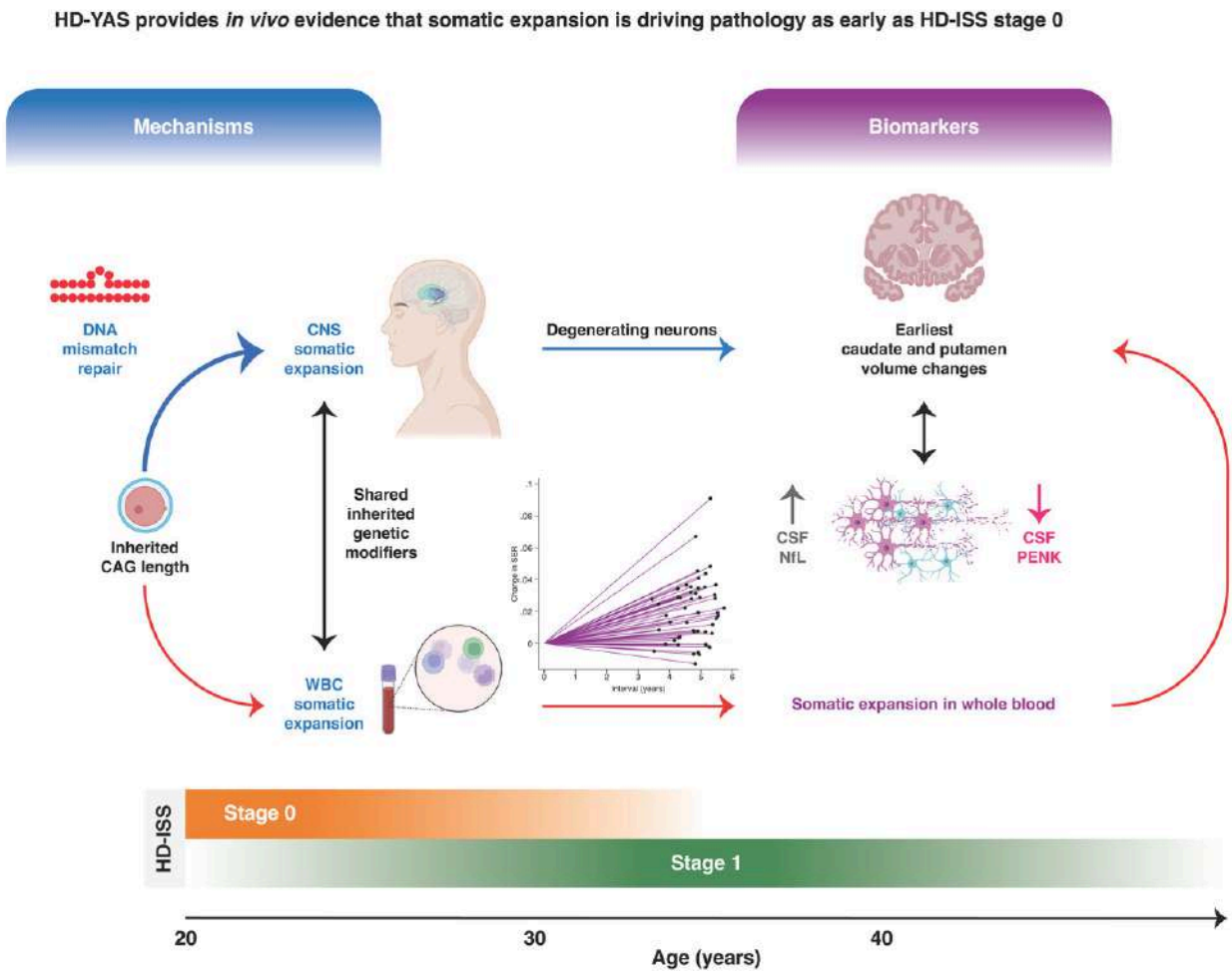
In **57 HD gene-expanded (HDGE)** individuals followed up over **~4.5 years,** the study team observed **no significant changes in functions** such as movement, thinking and behaviour. Compared to closely matched controls, these **functions remained normal up to two decades** before predicted motor onset of signs.

However, **subtle changes in the brain,** specifically in the **volumes of the caudate** and the **putamen** were detected. The **HDGE group** showed significantly **greater rates of atrophy** in those structures, as well as in the grey matter, white matter and whole brain, accompanied by higher rates of ventricular expansion.

Apart from brain atrophy, **changes in other markers of neurodegeneration** were observed: over ~4.5 years, the HDGE group had **higher levels** of cerebrospinal fluid neurofilament light chain **(CSF NfL),** a marker of neuronal health, as well as **reduced levels of CSF** proenkephalin **(PENK),** which is a marker of striatal neurons; in addition to that, **somatic CAG repeat expansion** measured longitudinally in blood was identified as a **predictor of the effect of CAG repeat length** on striatal markers of very early neurodegeneration.

References

1. Scahill, R. I., Zeun, P., Osborne-Crowley, K., Johnson, E. B., Gregory, S., Parker, C., ... & Tabrizi, S. J. (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.
2. Scahill, R. I., Farag, M., Murphy, M. J., Hobbs, N. Z., Leocadi, M., Langley, C., ... & Tabrizi, S. J. (2025). Somatic CAG repeat expansion in blood associates with biomarkers of neurodegeneration in Huntington's disease decades before clinical motor diagnosis. Nature Medicine, 1-12.



Graphical abstract showing pathways linking somatic expansion and its effects on different markers of neurodegeneration

The study was able to identify a **treatment window** where brain function is still normal, but very early and subtle changes in disease markers can be identified. The findings from HD-YAS could **help design and inform preventative trials** aimed at **slowing or stopping disease progression** from as early as **HD-ISS stages 0 and 1.**

Part of the HD-YAS team at our Investigators Meeting in London (UK) in May 2024
From left: Michael Murphy, Harry Knights, Rachael Scahill, Nicola Hobbs, Sarah Tabrizi, Douglas Langbehn, Mena Farag, Kate Fayer, Michela Leocadi.

Media coverage

- UCL press release
- HD-Buzz article on HD-YAS
- HDYO Breaking Down Barriers session

Prognostic enrichment for early-stage Huntington's Disease: an explainable machine learning approach for clinical trials

Mohsen Ghofrani-Jahromi

In this new edition, we are glad to feature a new study led by **Mohsen Ghofrani-Jahromi** (PhD candidate) from the **Georgiou-Karistianis Lab** at **Monash University** in **Australia** (see picture below), in collaboration with domestic and international experts. This work was published in **NeuroImage: Clinical** last year (2024).

The **added value** of this work is to introduce a **novel machine learning pipeline** to **predict ventricular enlargement** and therefore disease progression in early-stage HD participants **integrating structural MRI, genetic, motor, and cognitive data.**

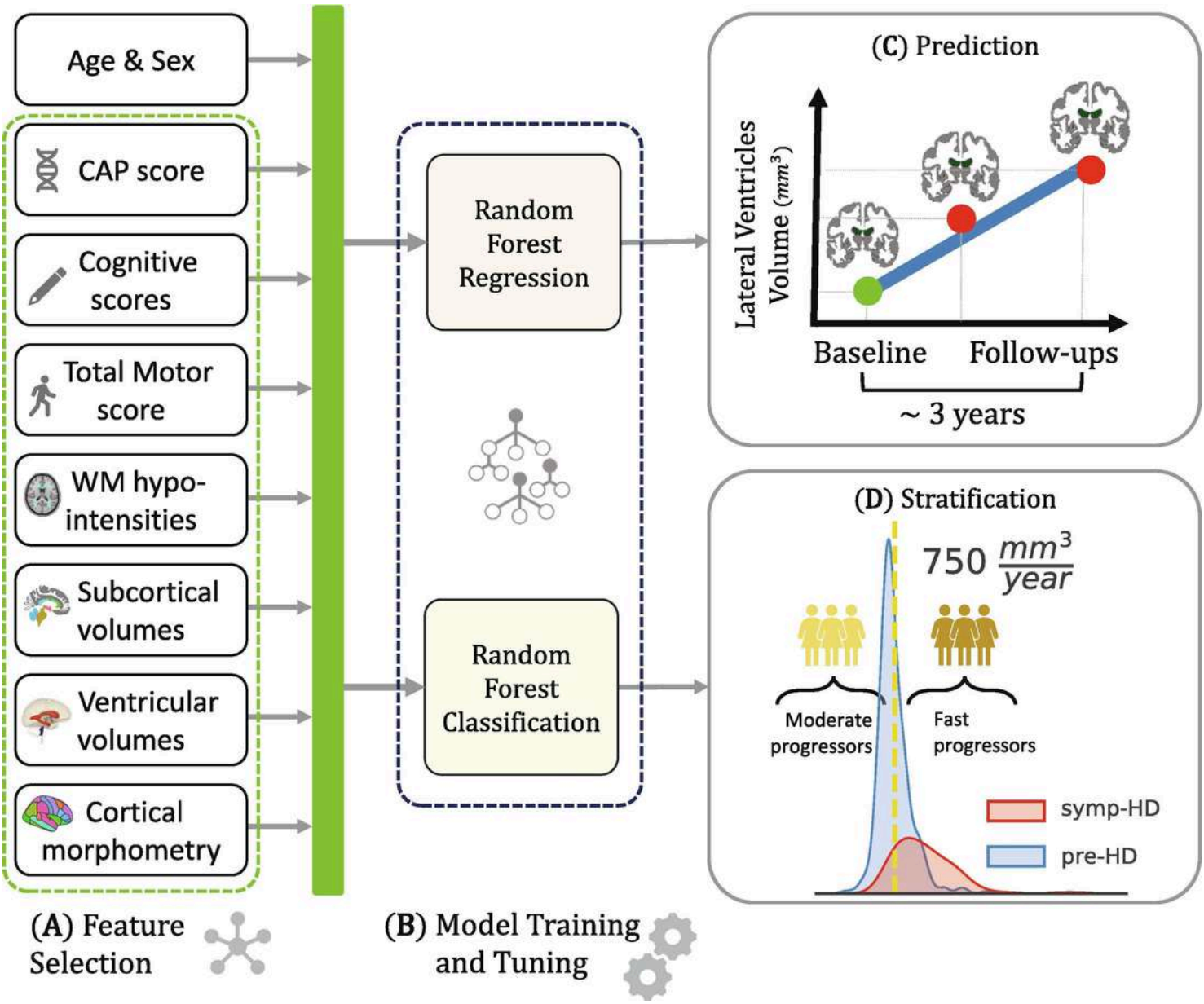
The research team used data from **451 gene positive HD participants** (both premanifest and manifest) from leading natural history studies **(PREDICT, TRACK, TrackON and IMAGE).**

This novel machine learning approach was able **to differentiate between low- and high-risk individuals** based on the rate of ventricular enlargement, which was also used as **target variable** for their **prognostic random forest regression models.**

This study was able **to identify high-risk individuals** with **81% accuracy,** and **enhance predictions of brain changes by 24%.**

Authors comment that their work is a major step towards **precision medicine,** enabling **earlier intervention,** better **clinical trial recruitment,** and **accelerated drug development** for HD.

The Nellie Georgiou-Karistianis Lab, Monash University, Australia



Overview of the pipeline for training the machine learning models for prognosis and stratification.

(A) Feature selection: biomarkers from different domains (listed above) were incrementally added to the input feature set and fed into the models for training. **(B) Model training and tuning:** random forest models were trained and evaluated on an independent test set for each subset of selected features. **(C) Prediction:** calculation of the rate of forthcoming lateral ventricular enlargement using linear regression analysis and selected as the ground truth for the prognostic random forest regression model. **(D) Stratification in two homogenous groups:** moderate progressors and fast progressors.

References

1. Ghofrani-Jahromi, Mohsen, Govinda R. Poudel, Adeel Razi, Pubu M. Abeyasinghe, Jane S. Paulsen, Sarah J. Tabrizi, Susmita Saha, and Nellie Georgiou-Karistianis. “Prognostic enrichment for early-stage Huntington’s disease: An explainable machine learning approach for clinical trial” NeuroImage: Clinical 43 (2024): 103650.

Highlights from the CHDI conference in Palm Springs, California
In-vivo PET/MR imaging in HD: longitudinal iMarkHD study

Dr Manuela Moretto

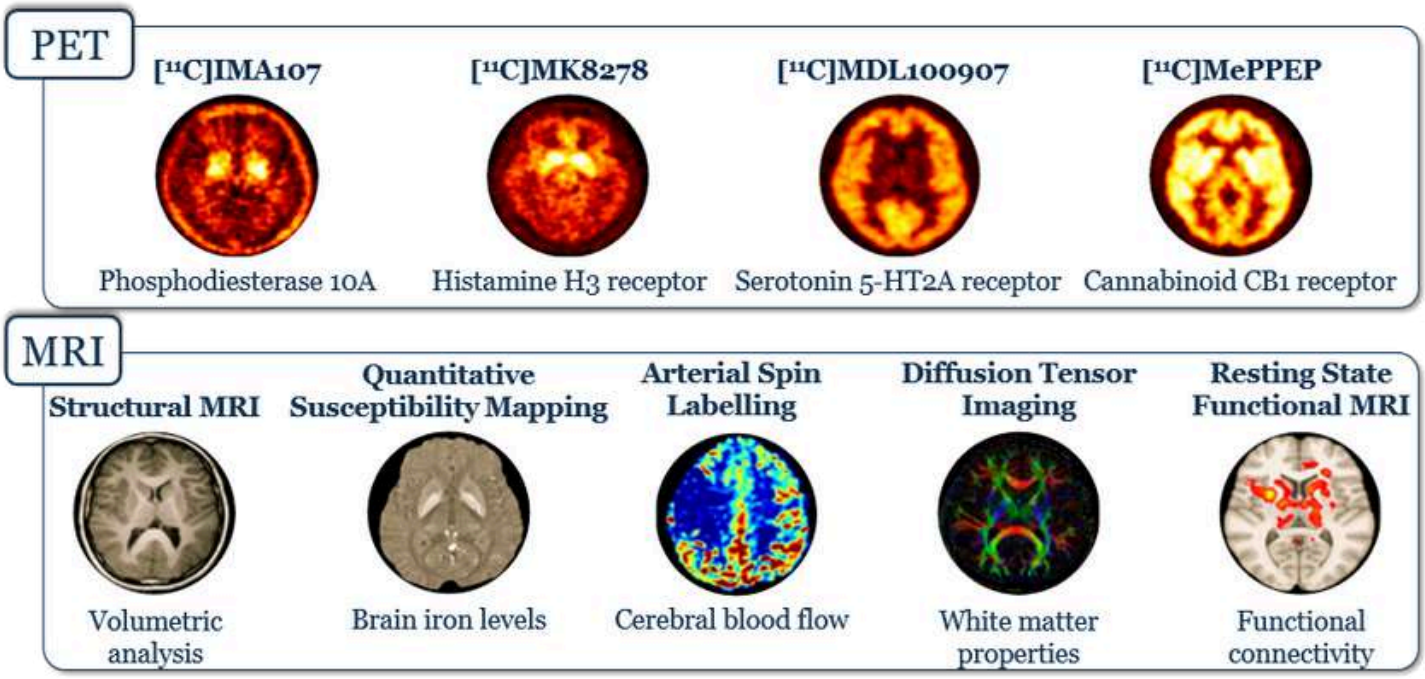
This month we are excited to feature the important work of **Manuela Moretto,** Postdoctoral researcher from the **Department of Information Engineering, Padova (Italy)** and **Neuroimaging Department, King's College London, London (UK) on the iMark HD study.**

The **iMarkHD In Vivo Longitudinal Imaging of HD pathology**, funded by **CHDI,** investigates changes in neuroimaging measures across different stages of HD and in controls.

The study uses **Positron Emission Tomography (PET)** and **MRI** to develop **biomarkers** for tracking HD progression and assessing treatment responses in future clinical trials.

The study employs a **multimodal neuroimaging approach,** combining **four PET tracers** – [11C]IMA107 (phosphodiesterase-10A activity marker), [11C]MePPEP (cannabinoid 1 receptor marker), [11C]MDL100907 (serotonin 2A receptor marker), and [11C]MK-8278 (histamine 3 receptor marker) – **with advanced MRI techniques** to assess brain volume **(T1w),** diffusivity **(DTI),** cerebral blood flow **(ASL),** iron deposition **(QSM),** and functional connectivity **(rs-fMRI).** Additionally, **biobank samples** and **comprehensive clinical assessments**– including cognitive, motor, neuropsychiatric, and functional evaluations –are collected.

Recruitment began in July 2023 and will conclude in July 2028, aiming for a final sample of **108 participants.** This includes 72 individuals with HD (PwHD) across different disease stages– pre-manifest (HD-ISS stage 0/1; N=24), peri-manifest (HD-ISS stage 2; N=24), and manifest (HD-ISS stage 3; N=24)– as well as 36 age- and sex-matched controls.



Summary of the different neuroimaging approaches in the iMark HD study
Rationale for PET targets: a) changes in PDE10A activity in the striatum may be one of the first detectable neuroimaging changes in premanifest PwHD; **b)** histamine has been suggested to play a role in neuronal and oxidative damage; **c)** decreased serotoninergic neurotransmission has been linked to depressive symptoms; **d)** the endocannabinoid system plays a role in neuroinflammation and neuroprotection, particularly in medium spiny neuron populations.

To date, **baseline PET and MRI acquisitions** have been **completed** for 23 pre-manifest PwHD, 21 peri-manifest PwHD, 23 manifest PwHD, and 34 HC, along with **1-year follow-ups** for 9 participants.

Interim cross-sectional analyses of PET tracer binding profiles in 16 pre-manifest PwHD and 23 HC revealed **strong group differences** for **[11C]IMA107** and **[11C]MK-8278** in regions including the **caudate, putamen, nucleus accumbens, and globus pallidus**, with **reductions observed in PwHD** compared to controls.

Findings on phosphodiesterase-10A binding align with a **previous human PET study (1),** which reported reduced phosphodiesterase-10A binding potential in pre-motor stage PwHD compared to HC in the striatum and globus pallidus. Additionally, interim results on this work provide the **first in vivo evidence of histamine 3 receptor binding reductions in pre-manifest PwHD** in regions corresponding to previously observed mRNA reductions in post-mortem tissues (2).
Further details on the iMarkHD study can be found **here.**

References

1. Fazio P, Fitzer-Attas CJ, Mrzljak L, et al. PET Molecular Imaging of Phosphodiesterase 10A: An Early Biomarker of Huntington's Disease Progression [published correction appears in Mov Disord. 2020 Dec;35(12):2363-2364. doi: 10.1002/mds.28367]. Mov Disord. 2020;35(4):606-615. doi:10.1002/mds.27963
2. van Wamelen DJ, Shan L, Aziz NA, et al. Functional increase of brain histaminergic signaling in Huntington's disease. Brain Pathol. 2011;21(4):419-427. doi:10.1111/j.1750-3639.2010.00465.x

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CHANGE OF DATE!!

Our next **iWG meeting** will be held remotely on:

Monday June 9th 2025

2:00-3:30 pm (BST)

3:00-4:30 pm (CEST)

For any queries, please get in touch:
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The first edition of the iWG newsletter can be found 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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