EHDN

iWG Newsletter

Edition 5 | March 2026

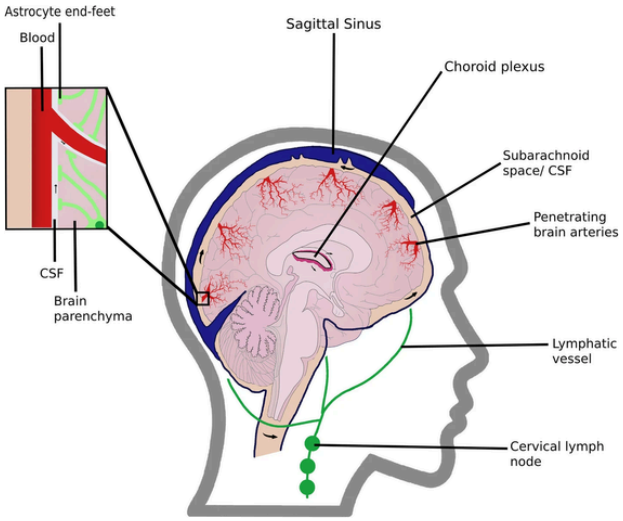
Dear reader...

Welcome to the fifth 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

Inside the brain "cleaning system": glymphatic cues for HD progression



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This edition highlights a 2025 review in the Journal of Huntington's Disease examining the role of the **glymphatic system** in HD.

The glymphatic system is **critical for clearing metabolic waste and neurotoxic proteins** from the brain, and its dysfunction might contribute to the **accumulation of mHTT** aggregates in HD.

The paper highlights how targeting glymphatic function through pharmacological or lifestyle interventions could offer new therapeutic strategies.
Its implications naturally extend to **neuroimaging research**, especially the **need to develop innovative and non-invasive imaging techniques** for tracking glymphatic function and possibly identify related biomarkers of HD progression.

Duan, W., Zhou, Y., & Liu, H. (2025). The glymphatic system in Huntington's disease. Journal of Huntington's disease, 14(3), 279-290. doi: 10.1177/18796397251331436.

Cerebrospinal fluid proenkephalin predicts striatal atrophy decades before clinical motor diagnosis in Huntington's disease

In this new edition, we are delighted to highlight a recent publication in **Movement Disorders (1)** led by our iWG member **Mena Farag** from University College London (UCL), jointly supervised by Rachael Scahill and Sarah Tabrizi.

This work saw contributions from the HD-YAS team at UCL, and collaborators at the University of Gothenburg, Sahlgrenska University Hospital and Glasgow.

Proenkephalin (PENK), an opioid peptide precursor highly expressed in striatal medium spiny neurons, represents a **promising candidate biomarker of striatal neuronal health**. Until now, however, its neuroanatomical specificity and value for distinguishing the earliest stages of HD had not been investigated.

Using unbiased **whole-brain voxel-based morphometry (VBM)**, this study shows that **lower baseline cerebrospinal fluid (CSF) PENK concentrations** are associated with subsequent **longitudinal brain volume loss** that is predominantly confined to the **striatum** bilaterally, in an HD gene-expanded group selected from the HD-YAS cohort approximately twenty years before predicted clinical motor diagnosis (Figure 2).

These relationships were robust over a mean follow-up of 4.9 years and remained significant independent of CAG repeat length and CAP100 score, indicating that

Mena Farag

CSF PENK reflects early striatal neurodegeneration beyond established predictors of disease progression.

By contrast, baseline CSF neurofilament light (NfL) was associated with more widespread atrophy, predominantly affecting cortical grey matter and widespread white matter pathways, in keeping with its role as an indicator of diffuse neuroaxonal injury.

Importantly, **CSF PENK demonstrated greater discriminatory performance than NfL in differentiating HD Integrated Staging System (HD-ISS) stage 0 from stage 1 (Figure 1)**, the latter defined by striatal volumes falling below age-adjusted normative ranges, with little added value from combining the two biomarkers.

(continue on next page)

Reference

1. Farag M, Murphy MJ, Hobbs NZ, Leocadi M, Fayer K, Thackeray O, Gobom J, Ciosi M, Heslegrave A, Zetterberg H, Langbehn DR, Monckton DG, Wild EJ, Tabrizi SJ, Scahill RI. Cerebrospinal Fluid Proenkephalin Predicts Striatal Atrophy Decades before Clinical Motor Diagnosis in Huntington's Disease. Mov Disord. 2025 Sep 26. https://doi.org/10.1002/mds.70062.

Cerebrospinal fluid proenkephalin predicts striatal atrophy decades before clinical motor diagnosis in Huntington's disease

Collectively, these findings position **CSF PENK as a sensitive and striatal-specific biomarker of very early HD-related neurodegeneration**, detectable decades before clinical motor diagnosis, and complementary to NfL. The results support its use alongside neuroimaging **to enrich HD-ISS stage 0 and 1 cohorts** for the design of preventive clinical trials in HD.

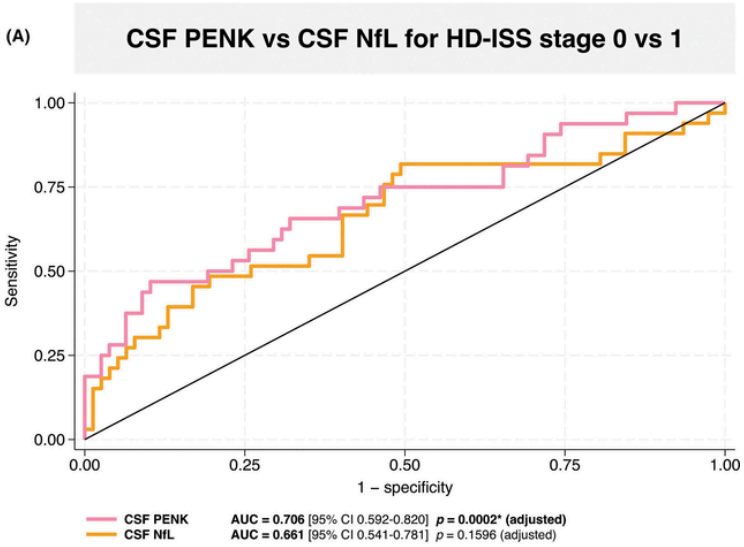


Figure 1. ROC curves for CSF PENK (pink) showing higher discrimination between HD-ISS Stage 1 and Stage 0 than CSF NfL (orange) from logistic regression models adjusted for age, sex and CAP100 score. Reproduced from Farag et al., Movement Disorders 2026, under a Creative Commons Attribution licence.

Mena Farag is a Specialist Registrar in Neurology who recently discussed and **successfully defended his PhD**, jointly supervised by Sarah Tabrizi and Rachael Scahill, and secondary supervisor, Edward Wild.

He joined the UCL HD Centre in August 2022, since then contributing to the HD-YAS study. Alongside his research role, he is involved in the clinical care of people with HD and in ongoing early-phase I-II clinical trials.

His doctoral work examines **longitudinal biofluid biomarkers and their associations with structural brain changes in HD gene-expanded young adults**.

He was recently **awarded the UK DRI PhD Prize** in December 2025 at Connectome 2025, which recognises doctoral researchers whose work has made a significant contribution to advancing the understanding of neurodegenerative diseases.

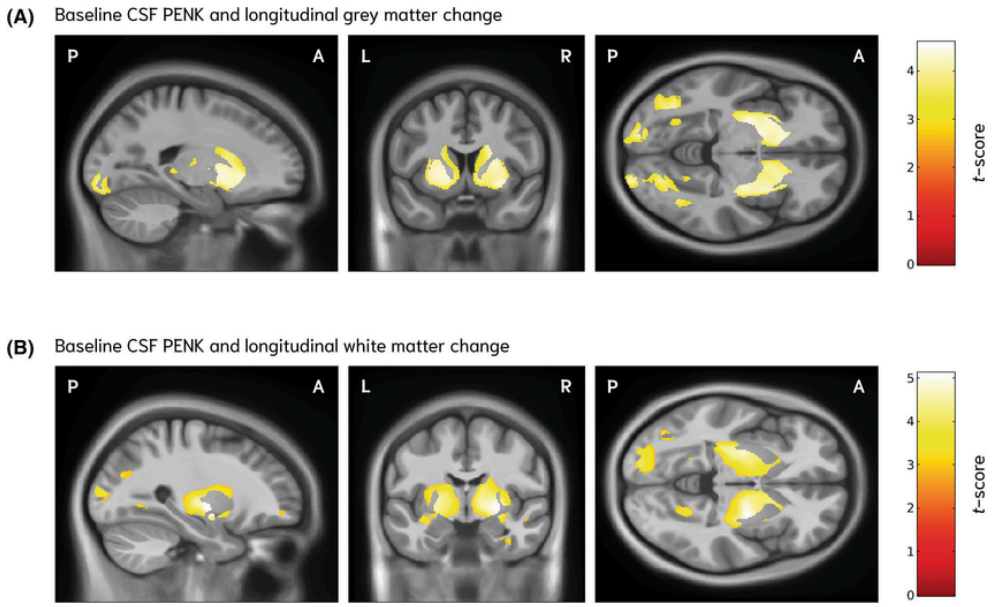


Figure 2. Associations between baseline baseline cerebrospinal fluid (CSF) proenkephalin (PENK) concentration and longitudinal grey (A) and white matter (B) volume change in the Huntington's disease gene-expanded (HDGE) cohort. Reproduced from Farag et al., Movement Disorders 2026, under a Creative Commons Attribution licence.

Disrupted sustained attention and altered functional connectivity in far-from-onset Huntington's disease gene-expanded young adults

We are glad to feature a recent study led by **Christelle Langley** from Cambridge University and published this year in **Alzheimer's and Dementia (1)**.

The study, which was a collaboration between Cambridge University and University College London, investigated **early cognitive and neural changes** in HD gene-expanded (HDGE) far from predicted clinical motor onset, focusing on sustained attention and its neural correlates.

Using longitudinal data from the **HD-YAS cohort**, the study examined 43 HDGE individuals who at baseline were on average 24 years from motor diagnosis and compared to 28 healthy controls.

Sustained attention was assessed using the **CANTAB Rapid Visual Information Processing (RVP) task**, alongside **resting-state fMRI** to examine functional connectivity (FC) within networks known to support sustained attention. Behavioural and imaging data were analysed cross-sectionally and longitudinally over a ~4.7-year follow-up.

HDGE participants showed significantly poorer sustained attention compared with controls, with **no evidence of longitudinal decline**, suggesting an **early and stable deficit rather than progressive deterioration (Figure 3)**. Importantly, this impairment was not attributable to motor slowing.

Christelle Langley

Altered associations between sustained attention and FC were observed in HDGE individuals, particularly involving **inferior frontal, parietal, occipital, and lentiform nucleus regions**, indicating disrupted integration within attention-supporting networks.

Longitudinal analyses further revealed **abnormal trajectories of network engagement** in HDGE compared with controls.

(continue on next page)

Reference

1. Langley, C., Leocadi, M., Hobbs, N.Z., Farag, M., Murphy, M.J., Fayer, K., Scahill, R.I., Rowe, J.B., Robbins, T.W., Tabrizi, S.J. and Sahakian, B.J., 2026. Discovery of disrupted sustained attention and altered functional connectivity in far-from-onset Huntington's disease gene-expanded young adults. Alzheimer's & Dementia, 22(1), p.e70944. https://doi.org/10.1007/s00259-025-07394-w

Disrupted sustained attention and altered functional connectivity in far-from-onset Huntington's disease gene-expanded young adults

In summary, this study provides the **first evidence that sustained attention is disrupted very early in HD** and is associated with **aberrant functional connectivity prior to motor onset**. These findings identify sustained attention and its neural substrates as potential early cognitive biomarkers and highlight the need for targeted interventions in the prodromal stages of HD.

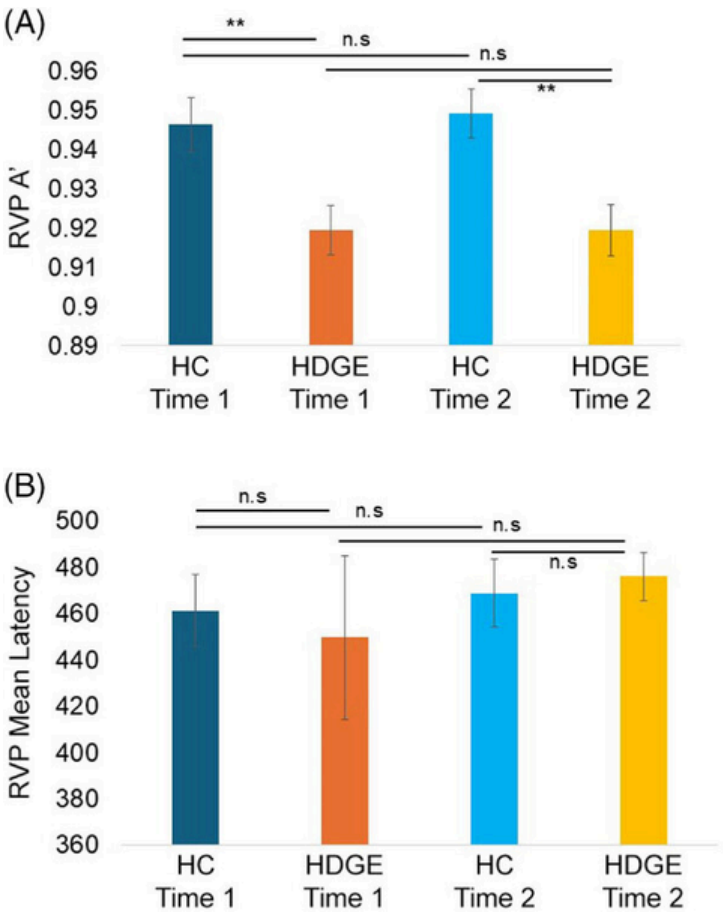
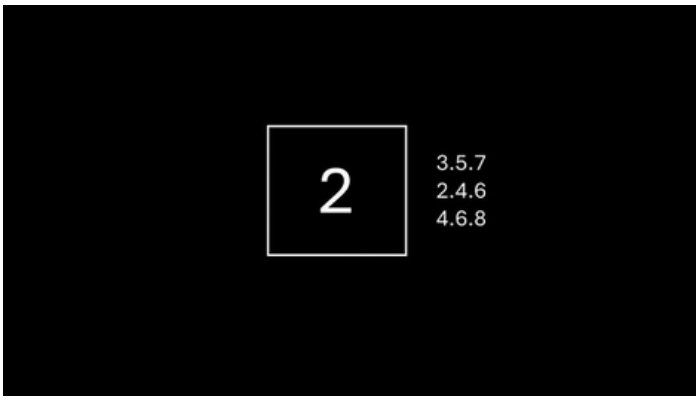


Figure 3. Performance on the CANTAB RVP task. (A) Sustained attention performance (RVP A'); (B) reaction time performance.



Schematic of the CANTAB RVP task

Christelle Langley is a cognitive neuroscientist and an **Assistant Research Professor** in the Department of Psychiatry at Cambridge University.

She completed her PhD at the University of Bristol and joined Cambridge in 2019, where her work spans **cognitive neuroscience, neuropsychology, neuropharmacology and neuroimaging**. She collaborates with researchers including Professor Sarah Tabrizi on the **Huntington's Disease Young Adult Study (HD-YAS)**, investigating early cognitive changes and neural network dysfunction in individuals far from clinical motor onset of HD.

Her HD research has contributed to understanding neural circuits, in particular fronto-striatal networks, and cognitive impairment before clinical motor onset.

Paediatric Huntington's disease brain changes: updates from the RAREST-JHD study

Umberto Sabatini's team (University Magna Graecia, Catanzaro)

Ferdinando Squitieri's team (LIRH Foundation, Rome)

In this edition, we are pleased to share recent updates from the **RAREST-JHD study**, which was featured in one of our previous editions.

The RAREST-JHD collaborative project (Ferdinando Squitieri, PI, LIRH Foundation, Rome, Italy and Umberto Sabatini, University Magna Graecia, Catanzaro, Italy) aims to study **clinical genetic changes and brain connectivity in paediatric HD**.

Initial evidence demonstrated that **paediatric-onset HD (POHD)** associated with highly expanded CAG repeats is characterised by **severe disease progression**, **reduced life expectancy**, selective striatal degeneration with relative preservation of cortical volumes, and **distinct biological alterations** underlying an atypical clinical presentation. These findings were derived from direct analyses of POHD cases, including ex vivo brain tissue and peripheral samples (1,2).

Although **these cases are exceedingly rare**, the retrospective study of these patients provided **crucial and invaluable insights into disease mechanisms**. Building on this foundational work and to characterise in vivo brain alterations, authors subsequently conducted **prospective studies** in rare POHD individuals who survived into adulthood and carried large CAG expansions (>60), using **simultaneous [^{18}F]FDG PET/MRI**.

References

1. Fusilli C, Migliore S, Mazza T, Consoli F, et al... Squitieri F. Biological and clinical manifestations of juvenile Huntington's disease: a retrospective analysis. Lancet Neurol. 2018 Nov;17(11):986-993. doi: https://doi.org/10.1016/s1474-4422(18)30294-1
2. Tramutola A, Bakels HS, Perrone F, Di Nottia M, et al... Squitieri F. GLUT-1 changes in paediatric Huntington disease brain cortex and fibroblasts: an observational case-control study. EBioMedicine. 2023 Nov;97:104849. doi: https://doi.org/10.1016/j.ebiom.2023.104849

Paediatric Huntington's disease brain changes: updates from the RAREST-JHD study

Cross-sectional and longitudinal quantitative imaging revealed **marked striatal volume loss and hypometabolism** in POHD brains, alongside distinctive alterations in **cortical and thalamic glucose metabolism** when compared with adult-onset HD patients (AOHD) with comparable clinical severity and disability. Furthermore, POHD confirmed preserved cortical thickness (3).

An update on these data which was recently published in Movement Disorders Clinical Practice highlighted **additional brain pathology in POHD** patient brains. Consistent with the predominant features of parkinsonism in POHD, **significant midbrain and substantia nigra volume loss** in this cohort was observed (Figure 4). Furthermore, **SN volume loss was linearly correlated with clinical parameters** in both the POHD and AOHD cohorts (Figure 5) (4).

This represents further evidence that **POHD with highly expanded and unstable mutations differs clinically and biologically from AOHD**. This analysis uncovers what is likely obscure in adult-onset HD and may offer clues to the interpretation of highly expanded CAG mutations as a driver of extended brain dysfunction and degeneration.

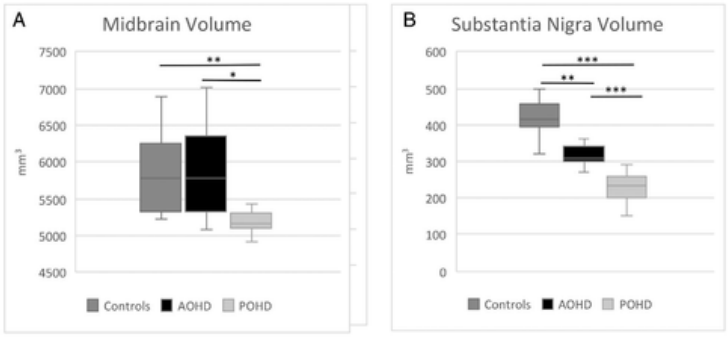


Figure 4. Midbrain (A) and substantia nigra (B) volumes in AOHD and POHD. Reproduced with permission from Movement Disorders Clinical Practice.

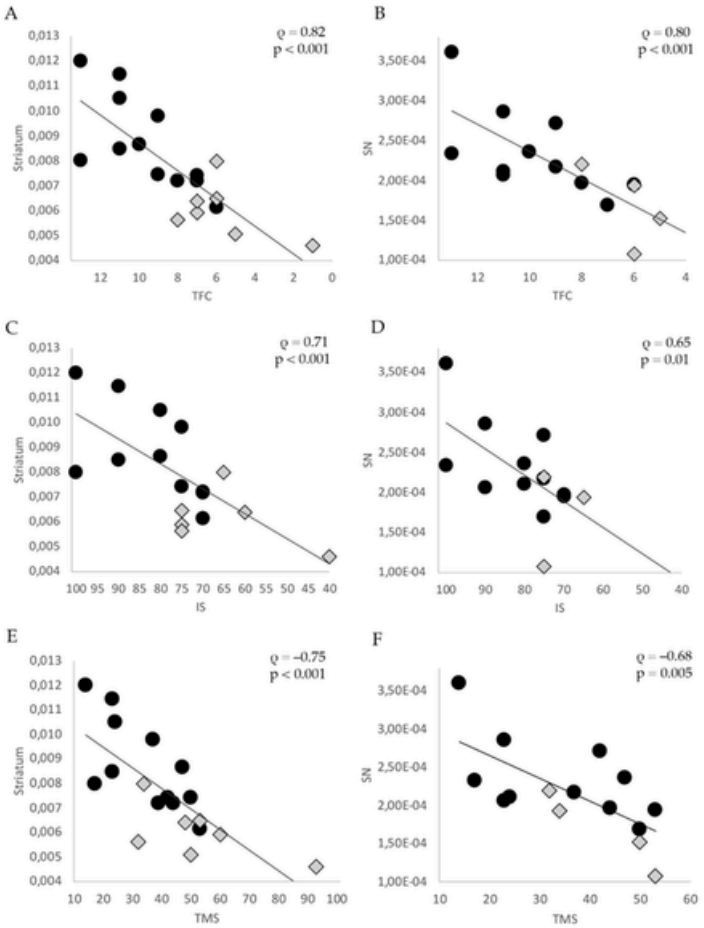


Figure 5. Correlations between SN, striatal volumes and clinical scores in POHD and AOHD (A-F). Reproduced with permission from Movement Disorders Clinical Practice.

References

3. Caligiuri ME, Tinelli E, Vizza P, Giancaterino G, Cicone F, Cascini GL, Sabatini U, Squitieri F. Pediatric Huntington Disease Brains Have Distinct Morphologic and Metabolic Traits: the RAREST-JHD Study. Mov Disord Clin Pract. 2024 Dec;11(12):1592-1597.
4. Sabatini U, Maffi S, Caligiuri ME, Sánchez-Castañeda C, Tinelli E, Squitieri F. Substantia Nigra as Brainstem Signature in Pediatric-Onset Huntington's Disease: The RAREST-JHD Study. Mov Disord Clin Pract. 2025 Oct 3.

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.

Previous editions can be found

HERE

Warm regards,

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