EHDN

iWG Newsletter

Edition 6 | August 2026

Dear reader...

Welcome to the sixth 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 Huntington's disease (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**

EHDN Imaging WG meeting: October 21st in Krakow, Poland

We are excited to announce that our next **EHDN Imaging WG meeting** will be held in person on Wednesday, October 21st, between 16:30-18:30, before the start of the EHDN Clinical Research Congress. The meeting is open to all iWG members. To confirm attendance, please email: **n.hobbs@ucl.ac.uk**.

- **Welcome**
  Nicola Hobbs & Rachael Scahill, UCL
- **Session 1: PET**
  - PDE10A and H3R density as early-stage PET biomarkers in HD: results from the iMarkHD study - Manuela Moretto, University of Padua & KCL
  - Multi-tracer PET reveals early disruption of cerebrospinal fluid dynamics in HD - Alex Calvano, KCL
- **Session 2: MRI**
  - Geometric properties of caudate and putamen mark the progression of HD - Dorian Pustina, CHDI
  - MRI biomarkers in HD clinical trials: what have we learned? - Marina Papoutsi, Ixico
- **Plans for 2026/2027, EHDN strategic fund application and final remarks**
  Nicola Hobbs & Rachael Scahill, UCL

No travelling subjects required: a new approach to image-level multi-site MRI harmonisation in Huntington's disease

We are delighted to highlight a recent pre-print, currently under review in **NeuroImage:Reports** (1) led by our iWG member **Annabelle Coleman** from University College London (UCL), jointly supervised by **Lauren Byrne**, **Rachael Scahill** and **Edward Wild**.

This paper shows how **mapping brain changes** across the full course of HD, from decades before diagnosis through to advanced disease (HD-ISS stages 0 to 3), requires **combining data across several studies** to get enough participants at each stage for reliable analysis. However, **different scanners introduce technical differences** that can influence downstream measures like brain volume, so data can't simply be combined without correction.

Superpixel-ComBat (SP-ComBat) (2) is an existing method for **removing these scanner effects** at the image level (correcting imaging intensity differences across scanners before downstream analyses, rather than adjusting the numbers calculated from images afterwards), but it normally depends on "travelling subjects": the same person scanned on every scanner involved. This is rarely available when combining data collected retrospectively.

This work adapts SP-ComBat to harmonise MRI data without travelling subjects. Instead, healthy controls matched by age and sex across scanners are used as **"pseudo-pairs"**, standing in for a travelling subject to estimate each scanner's specific effect **(Figure 1)**.

Annabelle Coleman

Applied to **548 participants scanned on six different scanners** across three retrospectively collected HD cohorts (**HD-YAS, HD-CSF, and TRACK-HD**), unpaired SP-ComBat harmonisation:

- Aligned image quality across scanners, reduced scanner-driven clustering, and aligned signal-intensity profiles across scanners: a principal component analysis showed the **proportion of variation explained by scanner identity dropped from 98% before harmonisation to 36% after harmonisation**.
- Resolved scanner-specific systematic segmentation errors **(Figure 2)**, **recovering ~30% of segmentations that would otherwise have failed quality control**, making it possible to use one unified analysis pipeline across every scanner rather than different tools site by site
- **Preserved**, and in some regions strengthened, **sensitivity to known HD-related brain changes**, including striatal atrophy in the earliest disease stages.

No travelling subjects required: a new approach to image-level multi-site MRI harmonisation in Huntington's disease

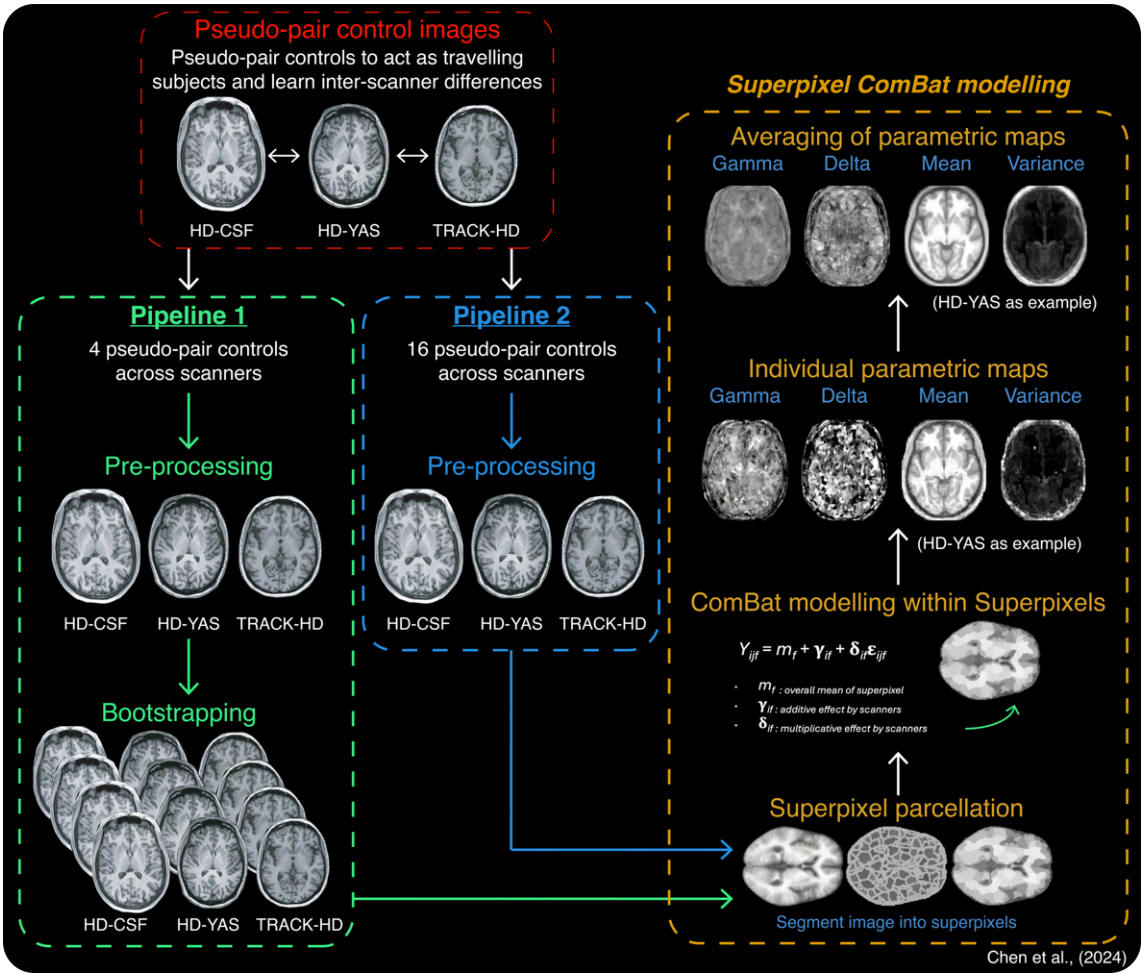

Figure 1: Overview of the unpaired SP-ComBat pseudo-pairing harmonization framework. Two pipelines were developed to estimate scanner effects using pseudo-paired healthy controls as surrogate traveling subjects. Pipeline 1 used four well-matched pseudo-pairs with an additional bootstrapping step to generate sufficient pseudo-pairs for scanner-effect estimation, whereas Pipeline 2 used 16 pseudo-pairs directly. Pseudo-pairs were pre-processed using CAT12 to standardize basic image quality and were registered to standard space through two-step spatial registration. SP-ComBat modelling followed Chen et al., 2024: 3D superpixel segmentation was applied to averaged pseudo-pair images, and ComBat modelling was used to estimate scanner effects within superpixels. Parametric maps were averaged at the group level and applied to perform site-effect removal for harmonization. Reproduced from Coleman et al., bioRxiv, 2026, with permission to reuse from corresponding author.

In conclusion, this method provided a **practical way to pool retrospectively collected, multi-site MRI data in HD** without needing dedicated travelling-subject scans, supporting larger and better-powered imaging studies going forward.

Annabelle Coleman is a **Research Fellow** and a **final-year PhD student** in the **Byrne Lab**. She started her journey in HD during her MSc at the UCL HD centre under the supervision of **Nicola Hobbs**.
Her PhD is focused on **characterising blood neurofilament light as a biomarker of HD**, from its earliest divergence to its structural brain correlates across the full disease course.

No travelling subjects required: a new approach to image-level multi-site MRI harmonisation in Huntington's disease

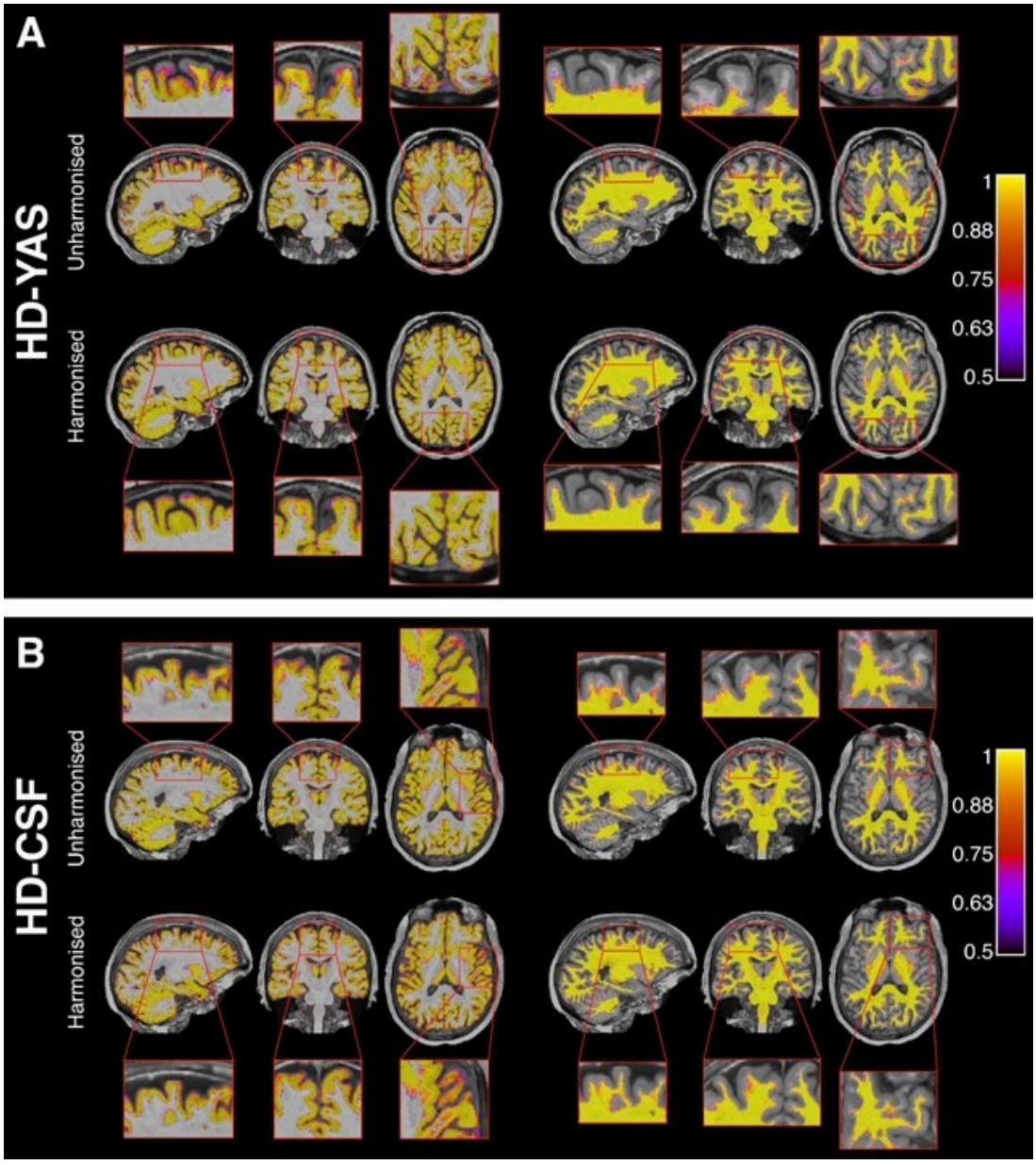

Figure 2: Effect of SP-ComBat harmonization on grey and white matter tissue segmentation in HD-YAS and HD-CSF scanners.

Grey and white matter segmentations overlaid on native-space T1W MRI for representative HD-YAS (A) and HD-CSF (B) scans before and after harmonization. Images are displayed in three-plane orthogonal view with representative sagittal, coronal, and axial slices. Both unharmonized and harmonized segmentations are overlaid on the harmonized T1W MRI to enable direct visual comparison on a common reference image. HD, Huntington's disease; HD-CSF, HD Cerebrospinal Fluid Study; HD-YAS, HD Young Adult Study. Reproduced from Coleman et al., bioRxiv, 2026, with permission to reuse from corresponding author.

References

1. Coleman, A., Chen, C.L., Hanson-Baiden, J., et al., 2026. Superpixel-ComBat multi-site harmonization of unpaired T1W MRI data in Huntington's disease. bioRxiv, pp.2026-05. DOI: https://doi.org/10.64898/2026.05.26.727928.
2. Chen, C.L., Torbati, M.E., Minhas, D.S., et al., 2024. Superpixel-ComBat modeling: A joint approach for harmonization and characterization of inter-scanner variability in T1-weighted images. Imaging Neuroscience, 2, pp.imag-2. DOI: https://doi.org/10.1162/imag_a_00306.

Changes in brain development set the stage for later brain degeneration

In this edition, we are also thrilled to feature a recent review authored by **Jordan Schultz** and **Peg Nopoulos** from the **University of Iowa** (1), which proposes a novel framework for understanding HD. This framework suggests that the **mutant huntingtin gene (mTT) may confer developmental advantages early in life**, while increasing vulnerability to neurodegeneration later, a concept known as **antagonistic pleiotropy (Figure 3)**.

Drawing on findings from the **Kids-HD study** (2), a study enrolling at-risk children and adolescents aged 6-25 years, the review reports that **children** and **young adults** carrying the HD gene expansion have been reported to show **larger cortical volumes**, **differences in cortical morphology**, and **advantages on cognitive measures** decades before expected symptom onset. However, these early benefits appear to be coupled with accelerated decline in brain regions particularly affected by HD, including the striatum. Furthermore, higher CAG repeats were also associated with larger cortical volumes and higher IQ scores (1) **(Figure 4)**.

The review argues that **mHTT may accelerate both brain development and brain aging**, providing a new way to connect neurodevelopment, neurodegeneration, and evolutionary biology in HD.

The Kids-HD study team

The Kids-HD study also demonstrated that **increases in brain volume were in cortical morphology measures** rather than cortical thickness, and specifically in surface area, folding and curvature index.

One important finding is that these **structural measures were positively correlated with the General Ability Index** (GAI), which is linked to IQ, supporting the view that increased surface area (which corresponds to increased number of cortical columns) is not due to pathological overgrowth, but rather to functional advantage and higher intelligence (1).

This framework could have important implications for the timing and design of future therapeutic interventions, hence replication and extension of findings is critically important.

References

1. Schultz, J.L. and Nopoulos, P.C., 2026. Early life functional advantage coupled with accelerated aging: The case for antagonistic pleiotropy in Huntington's disease. Journal of Huntington's disease, 15(2), pp.201-213. DOI: 10.1177/18796397251391069.
2. Lee, J.K., Ding, Y., Conrad, A.L., Cattaneo, E., et al., 2017. Sex-specific effects of the Huntington gene on normal neurodevelopment. Journal of neuroscience research, 95(1-2), pp.398-408. DOI: https://doi.org/10.1002/jnr.23980.

Changes in brain development set the stage for later brain degeneration

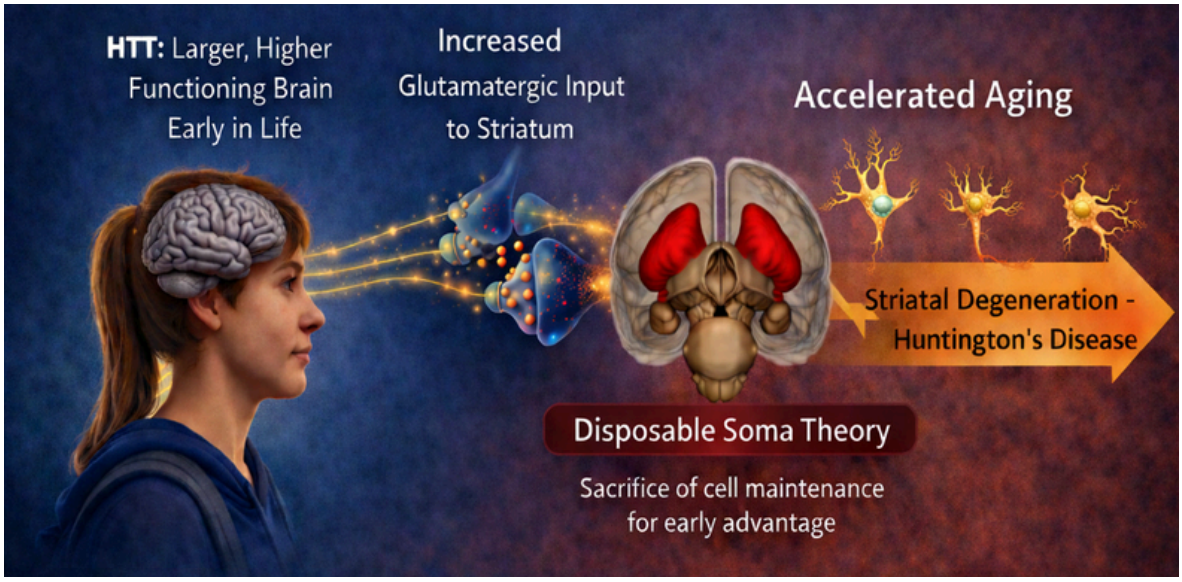

Figure 3: Antagonistic pleiotropy in HD.
Proposed novel framework: mHTT initially confers a developmental advantage by promoting a larger, more metabolically active cortex, consistent with the evolutionary role of huntingtin in human brain development. This early benefit is accompanied by a later-life liability, reflecting the principles of the Disposable Soma Theory. Specifically, investment in early brain growth occurs at the expense of long-term cellular maintenance, resulting in reduced resilience of DNA repair, proteostasis, mitochondrial function, and other stress-response pathways. Over time, these compromised maintenance systems become unable to withstand the metabolic demands of persistent glutamatergic activity, ultimately leading to excitotoxicity and neurodegeneration. Courtesy of Peg Nopoulos, University of Iowa.

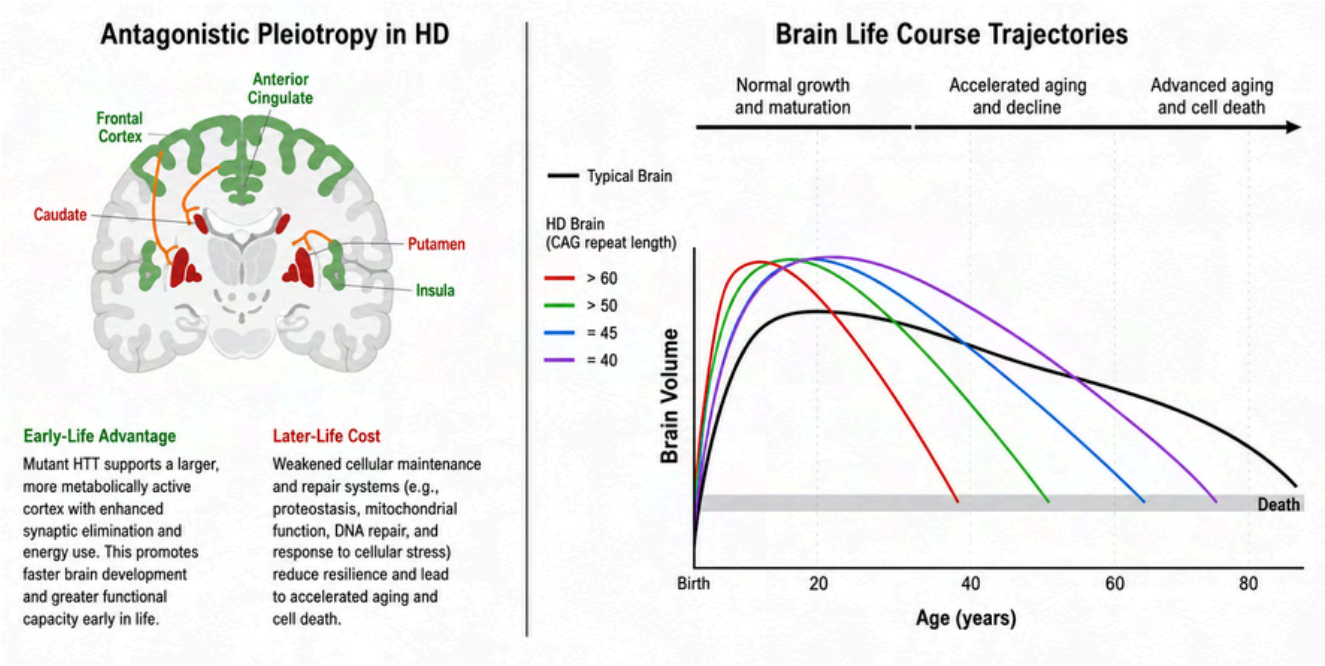

Figure 4: Early-life advantage vs later-life cost in HD and CAG-dependent different course trajectories.
In a CAG-dependent fashion, HTT drives accelerated brain development and maturation, tied with accelerated aging. This is driven by a larger cerebrum, with a cortex that is hyper-connected to the striatum, supplying excess excitatory input which is initially beneficial, and over time becomes toxic. Courtesy of Peg Nopoulos, University of Iowa, adapted from Schultz and Nopoulos, J Huntingtons Dis. 2026.

Abnormal cortical development sets the stage in Huntington disease

The NeuroGen Team at Paris Brain Institute
The team performs basic science and clinical studies thanks to the combined expertise of basic scientists, clinical research assistants and clinicians

We are glad to feature a recent review published in the **Journal of Huntington's disease (1)** by **Marine Degennaro, Sandrine Humbert and Mariacristina Capizzi** from the **NeuroGen team** at **Paris Brain Institute** which examines abnormal cortical development in HD.

HD typically has a **mid-adult onset**, although the causative gene is expressed from the earliest days of life. The gene encodes a protein that plays an important role in central cellular processes, including **intracellular transport and neuronal growth**.

Marine Degennaro

This raises the question of **whether early abnormalities during brain development might set the stage for later disease**.

Studies using human fetal samples, cellular models, and animal models have indeed shown that **neurodevelopment is altered in HD** (2,3).

Structural and **functional abnormalities** can be **detected prior to clinical motor diagnosis**, and mutation carriers may display subtle cognitive deficits, psychiatric disturbances, or motor impairments years before clinical diagnosis. However, despite these early developmental alterations and the lifelong presence of mutant huntingtin (mHTT), individuals carrying the HD mutation typically experience a long asymptomatic period.

References

1. Degennaro, M., Humbert, S. and Capizzi, M., 2026. Abnormal cortical development sets the stage in Huntington disease. Journal of Huntington's Disease, 15(2), pp.275-285. DOI: 10.1177/18796397261426033

Abnormal cortical development sets the stage in Huntington disease

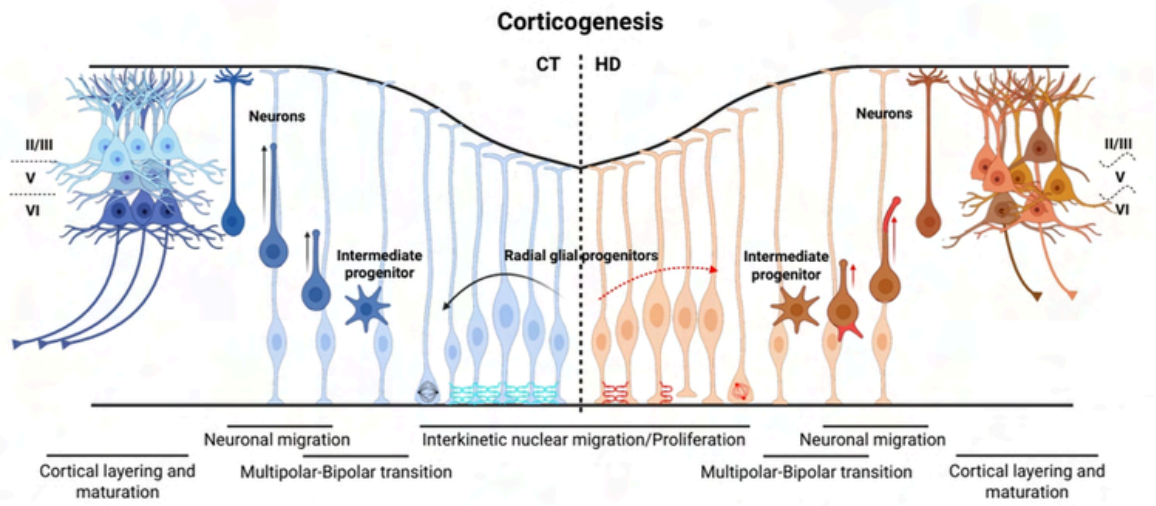

Figure 5: Corticogenesis is disrupted in Huntington's disease.
Schematic comparing the developmental trajectory of radial glial progenitors from the ventricular zone to the mature, layered cortex in control (CT, blue, left) versus HD (orange, right). In HD, junctional complexes at the apical endfeet of radial glial progenitors are loosened, promoting oblique/misoriented mitotic spindle orientation that favors premature differentiation over self-renewal. This is accompanied by a loss of apical-basal cell polarity and defects in axonal and dendritic growth in newly generated neurons, altering the normal course of neuronal migration, cortical layering, and maturation. II/III, V, VI: cortical layers. Adapted from Degennaro et al., 2026, with permission to reuse.

The authors provide an **overview of the functions of huntingtin** and the **dysfunctions** caused by **mutant huntingtin** or **huntingtin loss during development**, from **gastrulation** to **neurulation**. The specific contribution of the cerebral cortex to HD pathogenesis was examined also through the lens of **multi-omic evidence** revealing that HD cells undergo earlier but slower differentiation across developmental stages.

Huntingtin plays key roles in cortical development, including the **regulation of progenitor cell division**, the **migration of newly generated neurons**, and the **maturation of their somatodendritic compartments (Figure 5)**. In HD, **mutant huntingtin disrupts these developmental processes**, altering neuronal identity, cortical lamination, and circuit formation.

Importantly, studies in mice show that **early developmental defects** may **contribute to later neurodegeneration**.

Understanding these early developmental processes may help define a therapeutic window–a period of plasticity during which the **brain may still be able to correct or compensate for developmental abnormalities**.

References

2. "Developmental alterations in Huntington's disease neural cells and pharmacological rescue in cells and mice." Nature neuroscience 20, no. 5 (2017): 648-660. DOI: https://doi.org/10.1038/nn.4532.
3. Barnat, M., Capizzi et al., 2020. Huntington's disease alters human neurodevelopment. Science, 369(6505), pp.787-793. DOI: https://doi.org/10.1126/science.aax3338.

Abnormal cortical development sets the stage in Huntington disease

Sandrine Humbert and **Alexandra Durr** are **leaders** of the **NeuroGen Team at Paris Brain Institute**. The Neurogen team **investigates early stages of neurogenetic diseases including HD**, to identify mechanisms underlying clinical variability and **inform the development of future treatments**. The team focuses particularly on the **molecular mechanisms underlying abnormal brain development of the cortex in HD**.

Marine Degennaro is a **PhD student** who defended her thesis work in **June 2026**. Her thesis is titled **"Abnormal Huntington disease cortical development is associated with altered transcription and function of the Netrin1 pathway"**.

Mariacristina Capizzi is a **Senior Postdoctoral Fellow** working on **microtubule and actin cytoskeletal abnormalities during cortical development in HD**.

Second Run4HDYO event hosted in London

On Saturday, **July 4th 2026**, several members of the **iWG**, alongside friends from the **HD Centre UCL**, the **HD Youth Organization (HDYO)**, and the wider **HD community**, met up in **Battersea Park**, London, for the second annual **HDYO 5K run/walk 5K** to raise awareness on HD and funds benefitting the **Olivia (Liv) Martinez Scholarship Fund**.
This scholarship has been created in 2025 in memory of Liv, an HDYO ambassador whose passion, kindness, and strength touched so many lives.
The money raised (**more than £1700** 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 Barcelona 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.

Previous editions can be found

HERE

Warm regards,

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