EHDN

iWG Newsletter

Edition 1 | December 2024

Dear reader...

Welcome to the inaugural edition of the **Imaging Working Group (iWG) newsletter!**
This newsletter provides the latest **updates on imaging studies,** research **advancements,** and **innovative techniques** in **neuroimaging** that are transforming 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 EHDN & Enroll conference 2024 in Strasbourg (France)

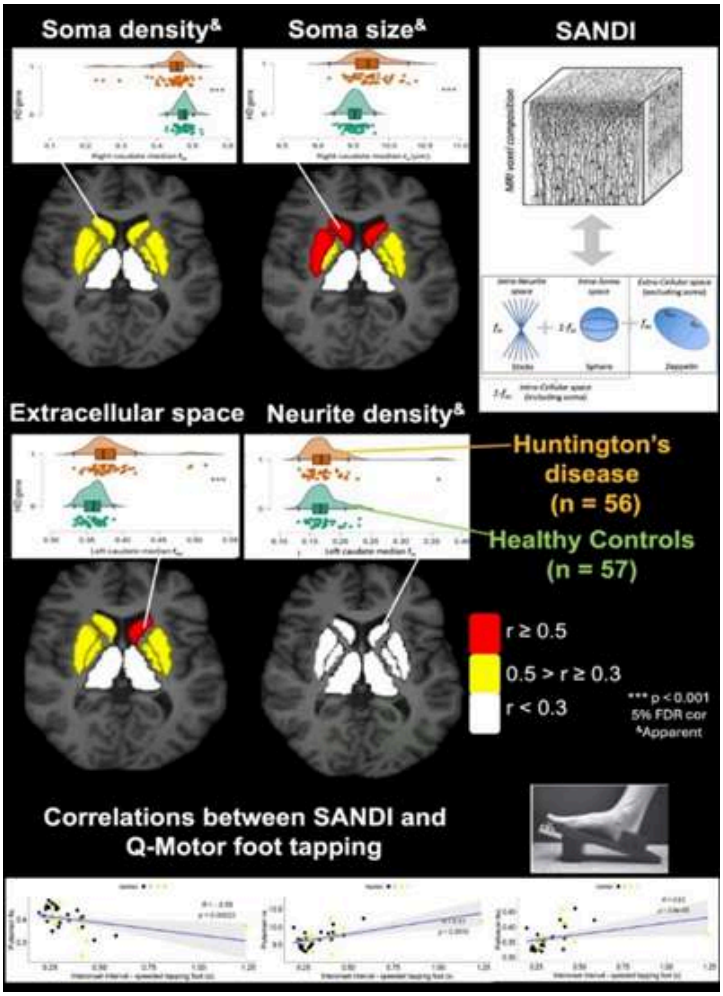
In **September,** many of us gathered at the recent **EHDN & Enroll Conference** in **Strasbourg,** where we held our **iWG meeting.** The meeting featured four outstanding presentations, each delivered by inspiring female scientists, showcasing the **latest advancements in imaging** within the field of HD. We are thrilled to highlight their work in the first part of the newsletter.

SAVE THE DATE!!
Next iWG meeting (remote)
Monday April 28th 2025
2:30-3:30 pm (BST)
3:30-4:30 pm (CEST)

In vivo mapping of striatal microstructure in Huntington's disease with Soma and Neurite Density Imaging (SANDI)

Claudia Metzler-Baddeley, *PhD*
Reader, Cardiff University Brain Research Imaging Centre (CUBRIC), UK

Claudia's work is centered around the exploration of whether advanced **multi-shell diffusion imaging using Soma and Neurite Density Imaging (SANDI)(1)** can detect striatal neurodegeneration in HD and identify **biomarkers** for clinical trials. SANDI's novelty lies in **incorporating soma size** and **density** alongside **neurite density.**



SANDI analyses from 56 HD patients and 57 controls revealed **lower apparent soma density and larger apparent soma size in HD patients' basal ganglia (2);** these metrics correlated with **motor impairments (Q-Motor foot tapping)(3),** explaining over 50% of striatal atrophy. SANDI indices hold potential as possible **in vivo biomarkers** for HD neuropathology and therapeutic evaluation.

The accompanying figure illustrates the SANDI brain microstructure model, highlighting group differences in SANDI indices.
Effect sizes are color-coded: red (large), yellow (moderate), and white (no effect).

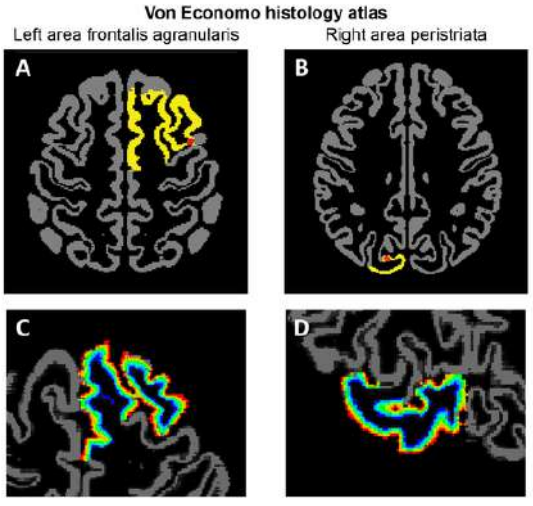
References

(1) Palombo et al. SANDI: A compartment-based model for non-invasive apparent soma and neurite imaging by diffusion MRI. Neuroimage 2020;215:116835. doi: 10.1016/j.neuroimage.2020.116835 [published Online First: 20200411]
(2) Ioakeimidis et al.. E005 In vivo quantification of basal ganglia microstructural abnormalities in Huntington's disease with soma and neurite density imaging. Journal of Neurology, Neurosurgery & Psychiatry, 2024, 95, Suppl 1, A47-A48.
(3) Reilmann R, Schubert R. Motor outcome measures in Huntington disease clinical trials. Handb Clin Neurol 2017;144:209-25. doi: 10.1016/B978-0-12-801893-4.00018-3

Differential cortical layer vulnerability in Huntington's Disease gene expansion carriers revealed by quantitative 7T MRI at 600µm isotropic resolution

Mitsuko Nakajima, *MBChB, BSc*
Clinical Research Fellow and PhD Candidate at Huntington's Disease Centre, Queen Square Institute of Neurology, London (UK)

Mitsuko's work is centred around combining **7T MRI** with **multi-parametric mapping (MPM)** to study the **distribution** and **extent of cortical layer pathology** in HD gene expansion carriers (HDGE).
Previous post-mortem studies showed that **selective atrophy** occurs in **layer 3 (L3)** and **L5** of the **primary motor cortex,** and **L3, L4** and **L6** of the **primary visual cortex** in advanced HD (1-2).
Using **voxel-based quantification analyses** to compare HDGE ~15 years from estimated onset (n=16) and matched controls (n=18), she revealed **clusters with lower proton density** in the **left frontal eye field (LFEF)** and **right visual area 6 (RV6)** (Figure, panels A-B). The largest effects were found in **L4** for both.



Histological layers were estimated using the Von Economo histology atlas (see Figure panels C-D).
For histological layers, **left frontalis agranularis (LFB)** had the **largest effect** in **layer III,** and in **right area peristriata (ROA), layer V.**

For the **first time in vivo**, Mitsuko's work demonstrated **differential cortical layer vulnerability in HDGE;** the results from ROA layer V are consistent with post-mortem studies (3). **Differences with quantitative MRI (qMRI) but not with volumetric MRI** support a **novel role for 7T qMRI** in cortical pathology examination in HDGE.

References

(1) Thu DCV, Oorschot DE, Tippett LJ, Nana AL, Hogg VM, Synek BJ, et al. Cell loss in the motor and cingulate cortex correlates with symptomatology in Huntington's disease. Brain. 2010;133(4):1094–110.
(2) Macdonald V, Halliday G. Pyramidal cell loss in motor cortices in Huntington's disease. Neurobiol Dis. 2002;10(3).
(3) Pressl C, Mätlik K, Kus L, Darnell P, Luo JD, Paul MR, Weiss AR, Liguore W, Carroll TS, Davis DA, McBride J, Heintz N. Selective vulnerability of layer 5a corticostriatal neurons in Huntington's disease. Neuron. 2024 Mar 20;112(6):924-941.e10. doi: 10.1016/j.neuron.2023.12.009.

Evaluating imaging biomarkers as potential surrogate endpoints

Marina Papoutsi, ***PhD***
Senior Biomarker Scientist at IXICO, London (UK)

In July 2024, a current **opinion paper** from our **EHDN iWG (1)** was published in the **Journal of Huntington's Disease** shedding light on the **utility** and **inclusion** of **neuroimaging** in clinical trials for HD. The paper by **Hobbs et al. (1)** (click **here**) emphasised the pivotal role of MRI, from **participant selection** to providing evidence of **disease modification** in the context of clinical trials; careful consideration is however required (e.g., regarding imaging modalities, study design, data analysis).

Complementary to this publication, **Marina** provided an **overview** of the important role of **imaging biomarkers in central nervous system (CNS) trials.**
Her presentation reviewed recent qualifications in **Alzheimer's disease and Amyotrophic Lateral Sclerosis**, using these as a foundation to discuss implications and challenges in HD.
She underscored the **complexities** introduced by **therapy side effects**, which can impact imaging analyses (e.g., volumetric and diffusion measures). These challenges can make **result interpretation** difficult and **hinder** the use of imaging biomarkers as **surrogate endpoints**.
Marina stressed that we are now at a **pivotal juncture in drug development** for HD, with many **clinical trials ongoing** or **scheduled.** There is a need to report, monitor and understand imaging-based changes, in order to adapt our methods accordingly.

Additionally, Marina discussed the implications of the **FDA's accelerated approval pathway,** which has promoted the use of biomarkers as primary/secondary endpoints in CNS clinical trials.
This pathway allows drugs to be marketed in the US **earlier,** pending the results of large confirmatory trials.
While the **EMA does not have an accelerated approval pathway,** it can grant **marketing authorization** under "exceptional circumstances", without comprehensive efficacy data.
Despite geographical limitations of the FDA's pathway, **its existence incentivises development in rare diseases, benefiting** the global patient **community**.

References

(1) Hobbs, Nicola Z. et al. 'Neuroimaging to Facilitate Clinical Trials in Huntington's Disease: Current Opinion from the EHDN Imaging Working Group'. 1 Jan. 2024 : 163 – 199.

Examining cognitive and motor network dysfunction in premanifest Huntington's Disease using neuro-navigated transcranial magnetic stimulation

Eva Woods, *BSc*
PhD candidate, Discipline of Physiology, Trinity College Dublin, Dublin (Ireland)

Eva and **Roisin**'s work focuses on investigating **interhemispheric connectivity** in preclinical HDGE using **dual-site paired-pulse transcranial magnetic stimulation (ds-ppTMS)** combined with **electromyography (EMG)** and **structural MRI (sMRI).**

Their study assesses **inhibitory** and **facilitatory interactions** between **motor, premotor,** and **dorsolateral prefrontal regions** via **the corpus callosum.**

Motor evoked potentials (MEPs) are recorded from the abductor pollicis brevis during ds-ppTMS, guided by neuro-navigated coil positioning for precise targeting.

Preliminary data from controls (n=16) show significant **interhemispheric inhibition** between **premotor** and **primary motor regions.** Data collection from HDGE (current n=3) is ongoing. Ultimately, the goal is to **integrate ds-ppTMS functional metrics** with **diffusion tensor imaging (DTI)** to explore **connectivity disruptions** in HDGE and how changes in functional connectivity relate to changes in structural connectivity.

This approach has the potential to **identify early, non-invasive,** and **cost-effective biomarkers** for HDGE, advancing the understanding and **early detection** of the disease.

Roisin McMackin, *PhD*
Assistant Professor in the Discipline of Physiology, Trinity College Dublin, Dublin (Ireland)

Kicking off new collaborations

At the EHDN, **neuroimaging findings in HD** were a **focal point** of many discussions, particularly regarding their role in **advancing therapeutic approaches.** The attention these findings received highlights their **growing importance** in our field.

During the iWG meeting, we mentioned that the plan for 2025 is **to kick off** a **new collaboration** between our WG and the **Advanced Therapies WG** (Lead Facilitator: William Gray).

The goal of this collaboration would be **to explore** whether existing **natural history imaging data** can be used to **inform gene-therapy trial design** in HD. Although our first meeting was thwarted by **Storm Bert,** we will be reconvening in **January 2025,** and we will provide an update in the next newsletter.

If you would like to be involved in this project, please email Nicola (n.hobbs@ucl.ac.uk).

Looking ahead

As we prepare for the new year, 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, I wish you all a **joyful holiday season** and a successful year ahead.

Thank you for your commitment to advancing imaging research and for being part of this vibrant community.

Warm regards,

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