

II-013: NfL concentration in CSF is a quantitative marker of the rate of neurodegeneration in aging and Huntington's disease: a semi-mechanistic model-based analysis

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Introduction and Objectives:

Neurofilament light chain (NfL) is a neuron-specific protein released into the cerebrospinal fluid (CSF) upon axonal damage or cell death. Increased NfL levels in CSF and plasma have been established as biomarkers of neurodegeneration, including in Huntington's Disease (HD). Moreover, in HD, NfL elevations correlate with cytosine-adenine-guanine (CAG) repeat length in the mutant huntingtin (HTT) gene.

We developed a novel semi-mechanistic model, which characterized the quantitative relationship between MRI measurements of whole brain volume and NfL concentration in CSF in healthy controls and HD mutation carriers using published data from a 24-month study involving an 80-participant cohort from ages 26 to 77 years (HD-CSF study, Rodrigues et al., 2020).

For model validation, predictions were compared to individual post-mortem brain mass data was obtained from 184 participants ranging in age from 20 to 100 years, with no prior history or pathological evidence of neurological disease (Svennerholm et al., 1997).

Methods:

The proposed semi-mechanistic model (Figure 1) was built on combined mass-balance principles and the following assumptions:

1. NfL exists only in neurons and is released only upon damage/death.
 2. Brain volume loss reflects neuron, glia and interstitial fluid loss.
 3. NfL concentration in brain tissue is the same for all subjects and homogenous throughout the brain.
 4. All released NfL enters CSF and is cleared by bulk CSF flow.
 5. CSF flow rates differ by disease state (values fixed from Hett et al., 2023).
- A population non-linear mixed effects (NLME) approach was used to estimate population parameters and inter-individual variability.

Whole brain volume modeled as:

$$V_{brain}(t) = k_0 + k_1 \cdot t - k_2 \cdot t^2$$

and the rate of neurodegeneration as:

$$-\frac{dV_{brain}}{dt}(t) = -k_1 + 2 \cdot k_2 \cdot t$$

where k_0 , k_1 and k_2 are the three polynomial coefficients. The effect of the number of CAG repeats on the neurodegeneration was implemented as:

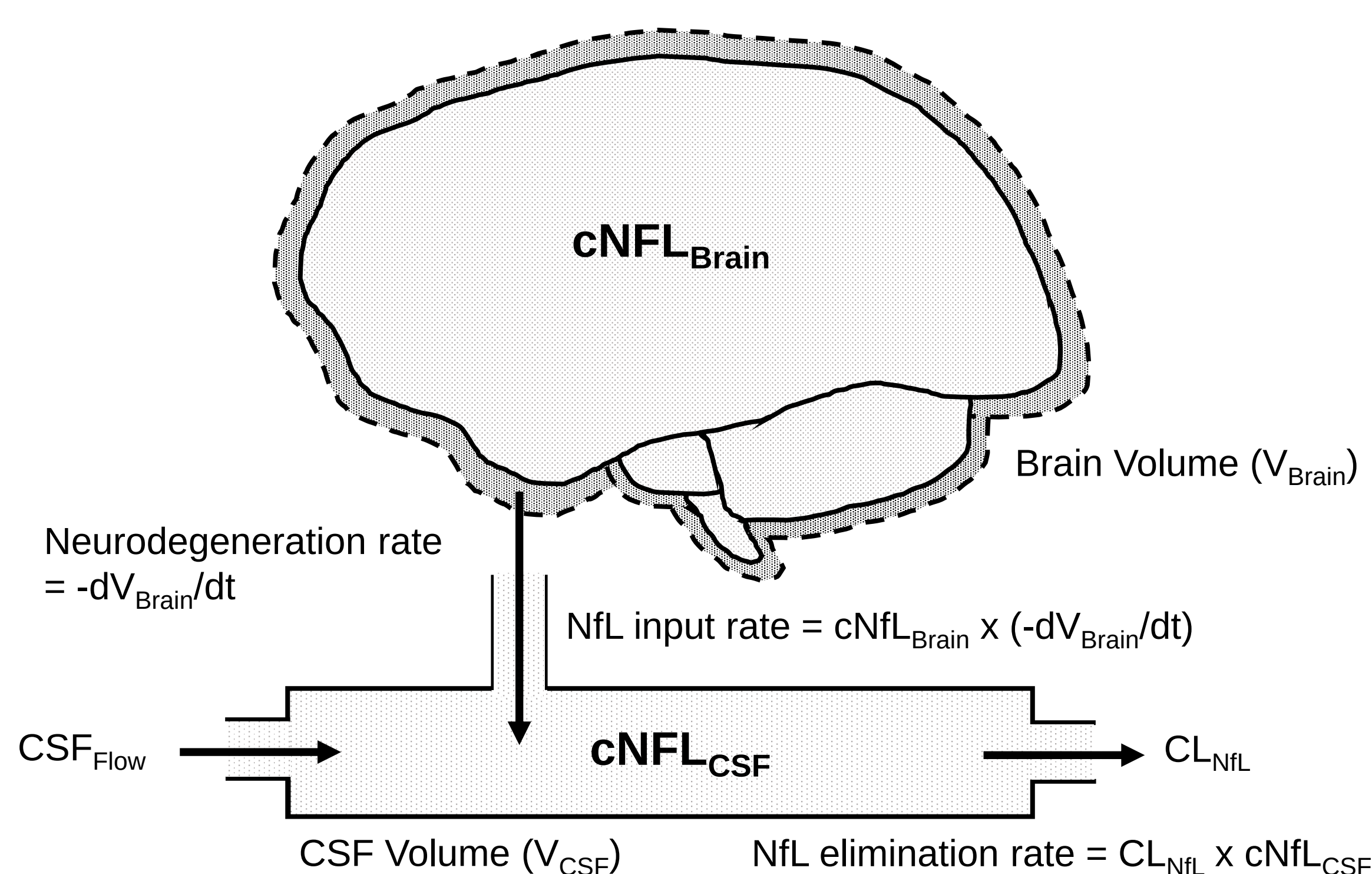
$$k_{2,HD,i} = k_{2,HD,Pop} \times \left(\frac{CAG_i}{42.5}\right)^{\beta_{CAG}}$$

for a typical individual of the HD population with CAG repeats = 42.5.

NfL concentration in CSF (assuming quasi-steady-state) was modeled as:

$$cNfL_{CSF}(t) = \frac{cNfL_{Brain} \cdot \left(-\frac{dV_{brain}}{dt}\right)}{CL_{NfL}(t)}$$

Figure 1: Conceptual model of NfL dynamics in the brain and CSF.



Results:

The model successfully described the brain volume changes (Figure 2) and the longitudinal trajectory of CSF NfL concentrations (Figure 3) in both HD patients and healthy controls. In HD subjects, the acceleration of neurodegeneration (k_2) increased with CAG repeat length, with $\beta_{CAG} = 2.74$. NfL concentration in brain tissue ($cNfL_{Brain}$) was estimated to 15.5 $\mu\text{g/g}$ (tissue density of 1.03 g/mL; Berger et al., 2017).

Model predictions of brain volume loss and CSF NfL dynamics were consistent with:

- Post-mortem brain mass data (Svennerholm et al. 1997) (Figure 4).
- Published experimental brain NfL levels: 10 - 47 $\mu\text{g/g}$ (Sjölin et al., 2022).

Figure 2: Observed (symbols) and predicted brain volume (median and 90th prediction interval) as a function of age for healthy controls, premanifest and manifest HD subjects.

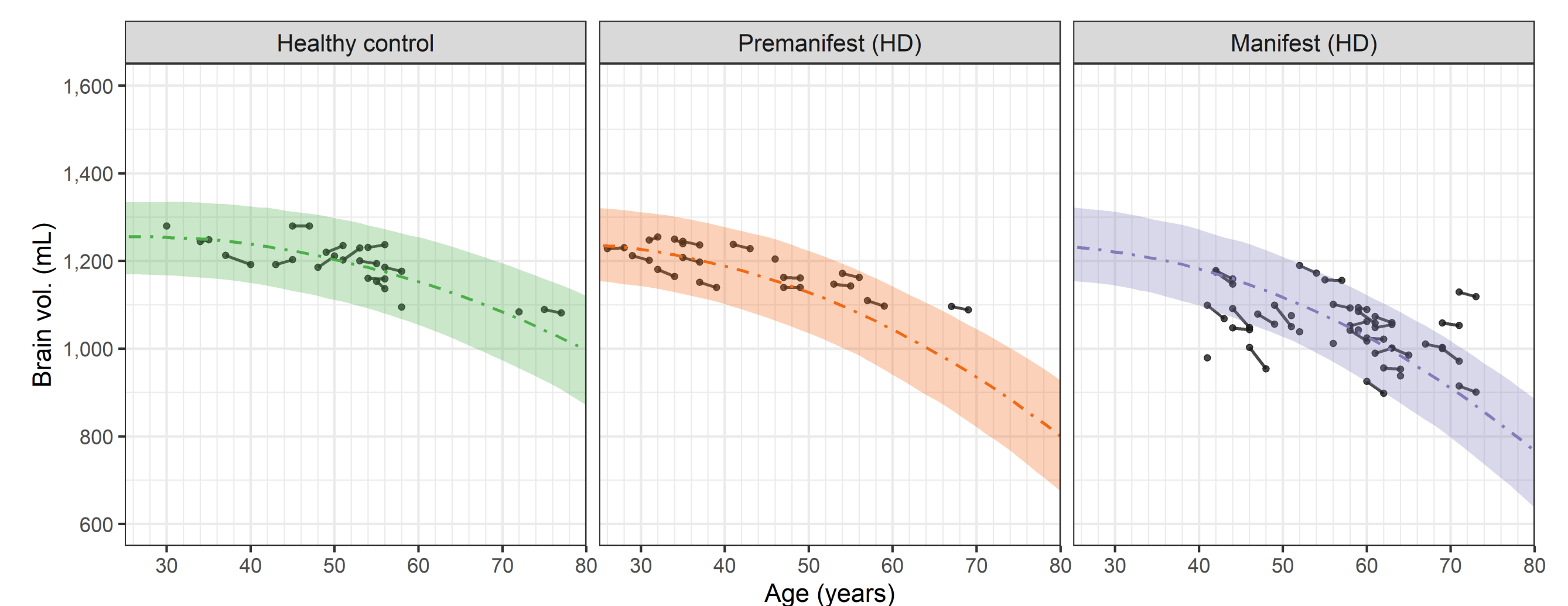


Figure 3: Observed (symbols) and predicted CSF NfL concentrations (median and 90th prediction interval) as a function of age for healthy controls, premanifest and manifest HD subjects.

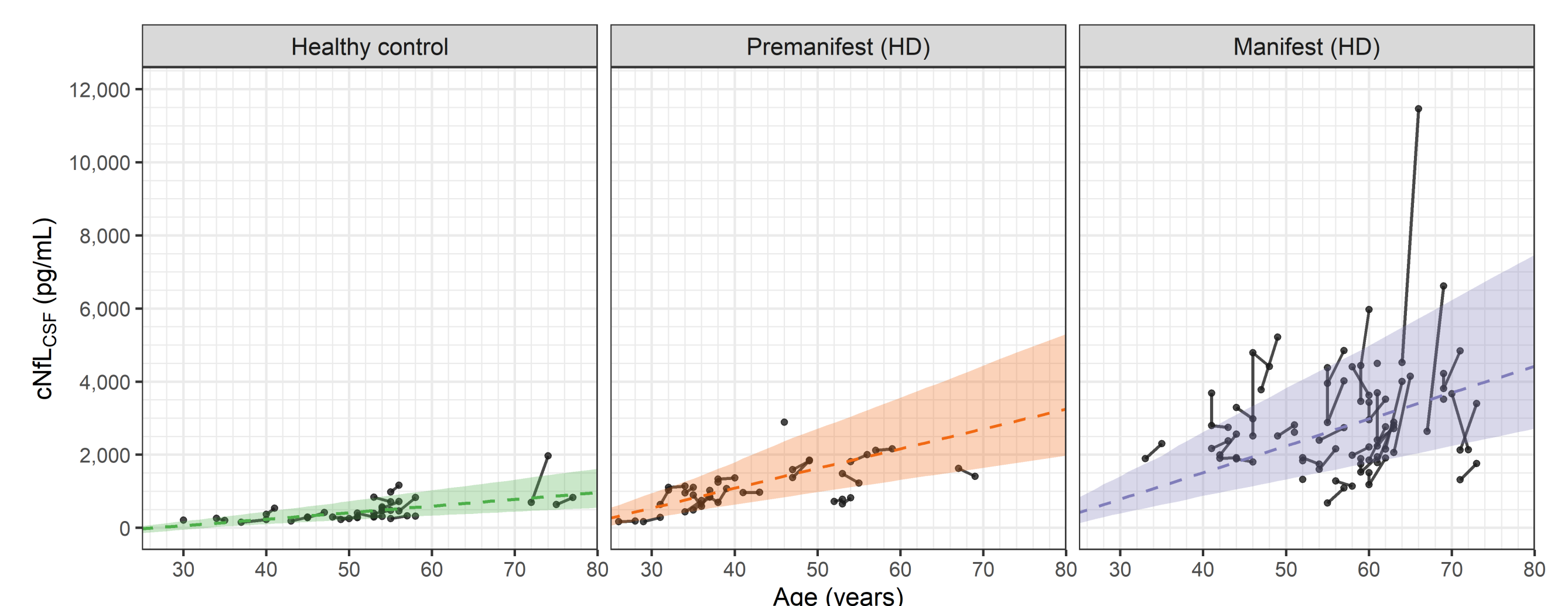
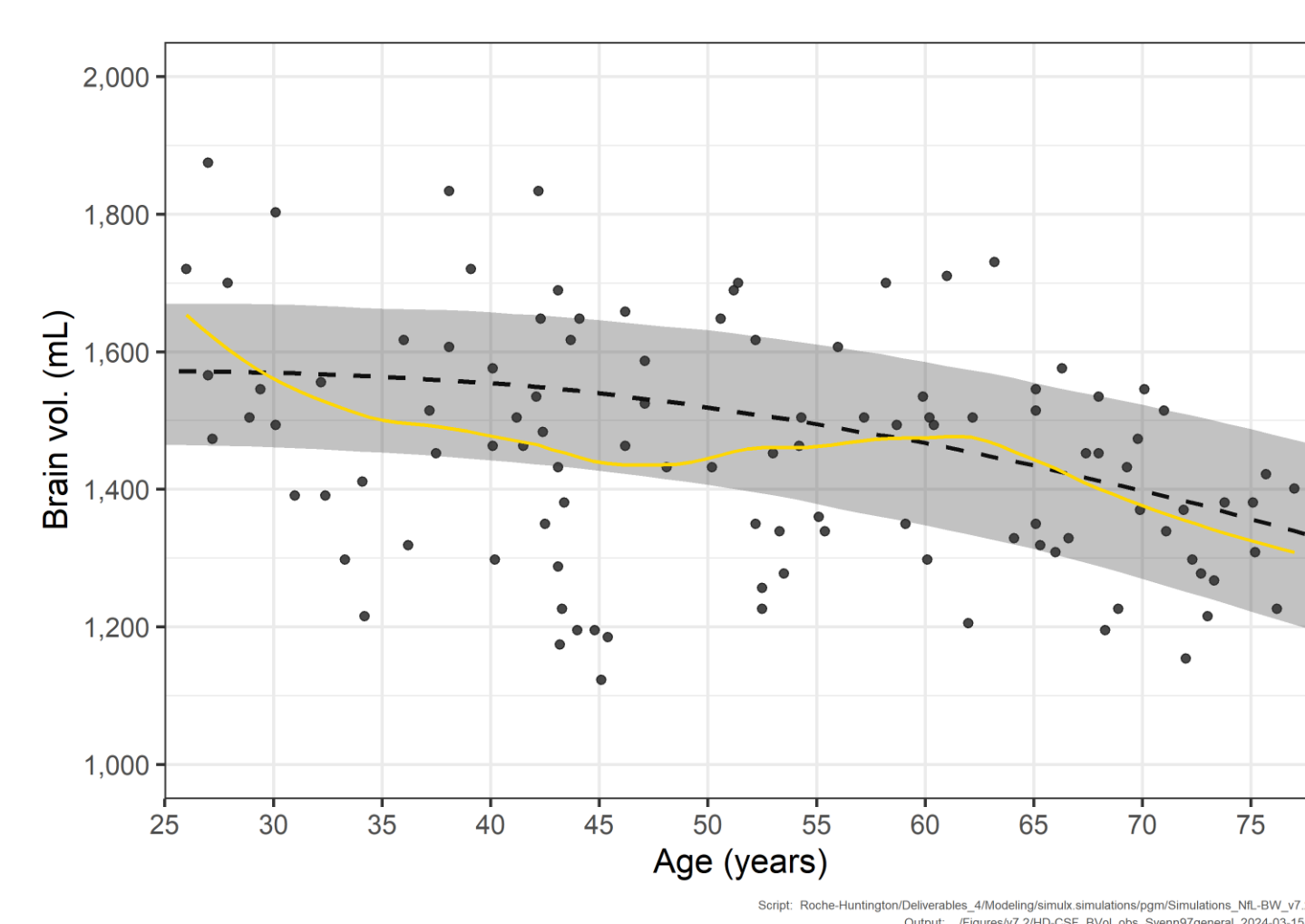


Figure 4: Model validation. Model predicted brain volume (median and 90th prediction interval) overlaid with the data from the Svennerholm et al. 1997 study and the spline function.



Conclusions:

- Our results support a mass-balance relationship between neuronal loss, brain volume shrinkage and CSF NfL levels in both healthy individuals and HD subjects.
- Findings suggest that bulk CSF flow is the dominant route for NfL elimination from the brain, with negligible immune system contribution under these conditions.
 - However, we acknowledge this mechanistic framework may not apply universally. In certain diseases, like Alzheimer's, increased microglial activation has been linked to low plasma NfL, suggesting that the immune system can modulate NfL clearance.
- The relationship between CSF NfL levels and the rate of release implies that NfL is a real-time marker of ongoing neuronal damage, rather than the extent of it.

Reference:

Machacek M, Garcia-Montoya E, McColgan P, Sanwald-Ducray P, Mazer NA. NfL concentration in CSF is a quantitative marker of the rate of neurodegeneration in aging and Huntington's disease: a semi-mechanistic model-based analysis. *Front Neurosci.* 2024 Jul 3;18:1420198.

