Evidence of Antagonistic Pleiotropy: Somatomotor and Frontoparietal Network Corticostriatal Hyper-Connectivity in Huntington's Disease Gene-Expanders

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Introduction

- **Antagonistic Pleiotropy – the hypothesis that a gene confers both advantages and disadvantages (Williams, 1957, *Evolution)*.**
- Huntington's disease (HD) is traditionally characterized as a neurodegenerative disease (the HDCR Group, 1993, *Cell*).
- Recent evidence, however, suggests that increased CAG repeats (≥ 40 CAG repeats) confers structural and cognitive advantages early in life (Neema et al., 2024, *Ann. Neurol*).
- Neurodevelopment and neurodegeneration may in HD may be driven by hyper glutamatergic neurotransmission via corticostriatal pathways (DiFiglia, 1990, *TINS*).
- **Knowledge gap**: The effects of CAG trinucleotide gene expansion on functional neurodevelopment are unclear.

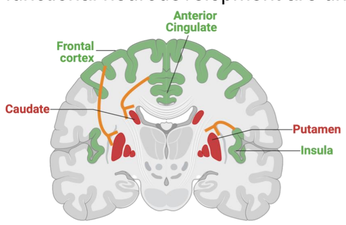


Figure 1. Hypotheses. Because the frontal cortices have the densest striatal connections (Carman et al., 1965, *J Neurol Neurosurg Psychiatry*; Donoghue and Herkenham, 1986, *Brain Res*; Chikama et al., 1997, *J Neurosci*), we predict that genepanded (GE) individuals will show increased and decreased rsFC in the somatomotor and frontoparietal networks during neurodevelopment and neurodegeneration, respectively, relative to gene nonexpanded (GNE) individuals.

Methods

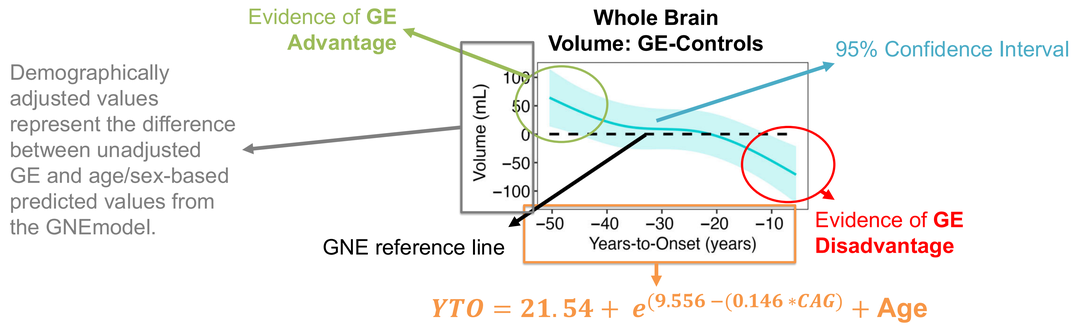
Childhood to adult neurodevelopment in gene-expanded Huntington's disease (ChANGE-HD)

- The first prospective, multi-site observational trial to systematically document brain structure and function during the premanifest phase of HD in children and young adults.
- Participants aged 6-30 years who are at risk for HD.
- At each visit, cognitive, motor, behavioral, blood, and MRI data are collected.

Site	*Group*	*N*	*Age*	*Right-handed*	*Female*	*CAG Repeats*
CHOP	GE	89	23.13±5.53	67	62	45.15±3.59
	GNE	59	21.94±6.32	35	39	19.53±3
Columbia	GE	51	22.15±6.07	27	40	45.65±4.8
	GNE	58	21.4±5.35	23	43	20.07±4.53
Iowa	GE	108	21.52±6.03	68	76	44.3±4.23
	GNE	146	19.18±5.93	81	84	19.58±3.62
UC Davis	GE	40	21.86±7.2	23	20	43.3±3.64
	GNE	51	19.28±6.83	28	35	20.67±4.02
UT Houston	GE	43	17.35±8.44	23	27	45.84±5.39
	GNE	81	16.32±4.95	51	48	20.38±3.51
Vanderbilt	GE	48	19.32±6.67	27	34	46.52±4.64
	GNE	47	17.88±7.21	18	32	19.68±2.62
Total	-	821	-	471	540	-

Table 1. Interim demographic data for ChANGE-HD study. Data are stratified by data-collection site and group (GE vs. GNE). Error values represent standard deviations. CHOP = Children's Hospital of Philadelphia

The Years-to-Onset Model



$$YTO = 21.54 + e^{(9.556 - (0.146 * CAG)} + \text{Age}$$

Figure 2. Example illustration of YTO model results from Neema et al. (2024; *Annals of Neurology*).

Results

Hyper striatal-somatomotor network rsFC in GE

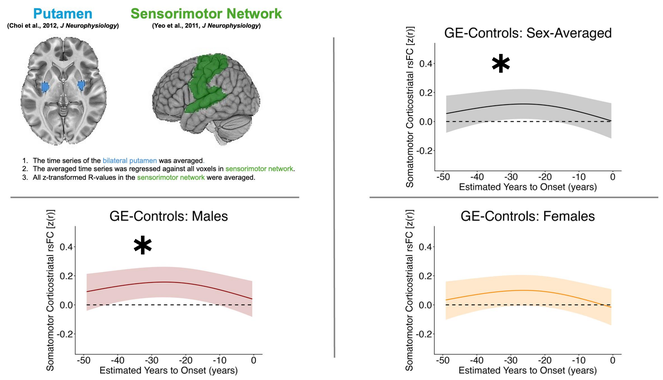


Figure 3. Years-to-onset (YTO) dependent Striatal-somatomotor rsFC changes in GE participants throughout the premanifest course of HD. * – p < 0.05.

Hyper striatal-frontoparietal network rsFC in GE

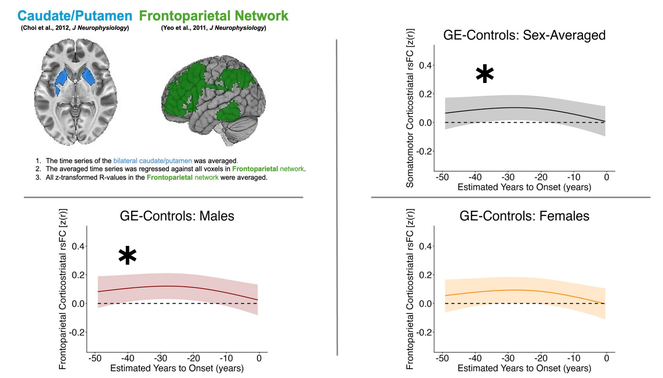


Figure 4. Years-to-onset (YTO) dependent Striatal-frontoparietal rsFC changes in GE participants throughout the premanifest course of HD. * – p < 0.05.

Result (cont.)

No difference between GE and GNE DMN, VAN, and Limbic rsFC

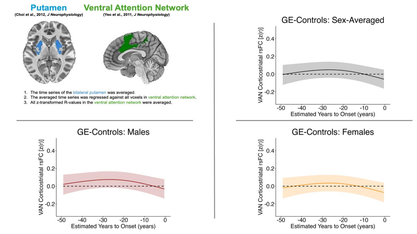


Figure 5. Years-to-onset (YTO) dependent Striatal-VAN rsFC changes in GE participants throughout the premanifest course of HD.

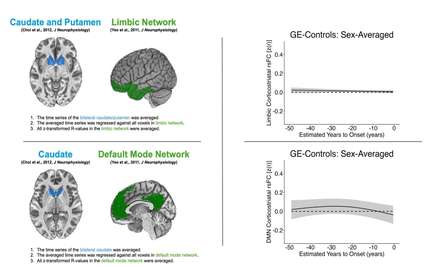


Figure 6. Years-to-onset (YTO) dependent striatal-limbic (top) and striatal-DMN (bottom) rsFC changes in GE participants throughout the premanifest course HD.

Summary

- Expansion of the CAG Trinucleotide on Chromosome 4 (Exon 1) is associated with increased Somatomotor and Frontoparietal network rsFC between 35 and 15 years before HD motor symptom onset
- These effects are primarily driven by males.
- We observed no evidence of this effect in other networks (e.g., VAN, DMN, and Limbic).
- We observed no evidence of neurodegenerative effects on rsFC (closer to motor symptom onset).

Take-home message

CAG trinucleotide overexpansion drives hyper-connectivity of the somatomotor and frontoparietal networks during neurodevelopment

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